Federated analyses using MS registry data

PhD Lars Forsberg, Karolinska Institutet, Sweden

More Europa Webinar 4: Understanding real world drug effects by performing federated analyses across four national multiple-scerosis registries

Federated analyses using MS registry data

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Run statistical analysis and machine learning algorithms between data sources without merging data

More Europa Webinar 4: Understanding real world drug effects by performing federated analyses across four national multiple-scerosis registries

Federated analyses using MS registry data

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Case study for federated learning: Relapse difference between treatment arms

More Europa Webinar 4: Understanding real world drug effects by performing federated analyses across four national multiple-scerosis registries

Multiple Sclerosis

- Chronic autoimmune disease where the immune system attacks the myelin in the white matter, causing lesions in the brain or in the spinal cord.

- Prevalence of MS is 0.2%.

- If a lesion causes a clinical brain dysfunction, this is known as a relapse. MS patients with relapses have Relapsing Remitting MS (RRMS).

- The brain may recover from a relapse after some months and regain function

- Some damages may remain (70% of all lesions remain as scars)

- The disease may develop into a progressive course with or without relapses. This is called Secondary Progressive MS (SPMS). No effective treatment available.

- Some patients get progressive MS from the start: Primary Progressive MS (PPMS)

- MS leads to a wide range of symptoms: fatigue, visual disturbances, walking difficulties, cognitive issues, etc.

1868

Jean Martin Charcot

Established Multiple Sclerosis as a disease of the nervous system that may follow a progressive course

Zalc, B. One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease. Brain 141, 3482–3488 (2018).

1955

Douglas McAlpine

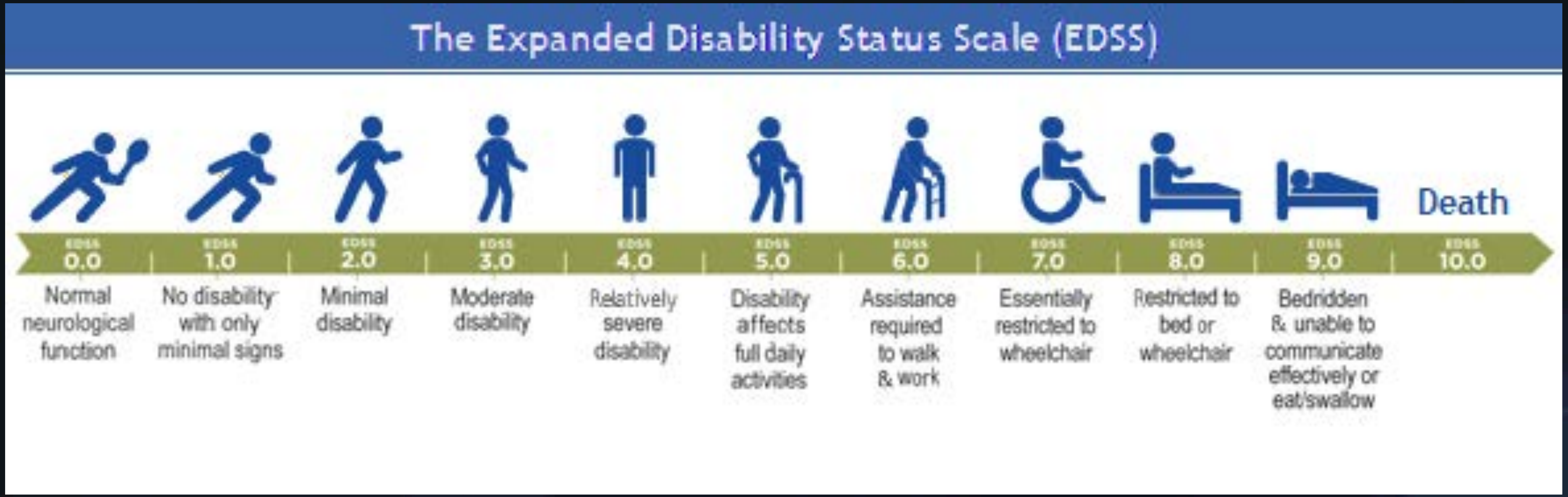
Formally described three major MS subtypes,

Relapsing Remitting MS (RRMS)
Secondary Progressive MS (SPMS)
Primary Progressive MS (PPMS)

McAlpine, D., Compston, N. & Lumsden, C. Course and prognosis of multiple sclerosis. Multiple sclerosis 135–155 (1955).

1955, 1983

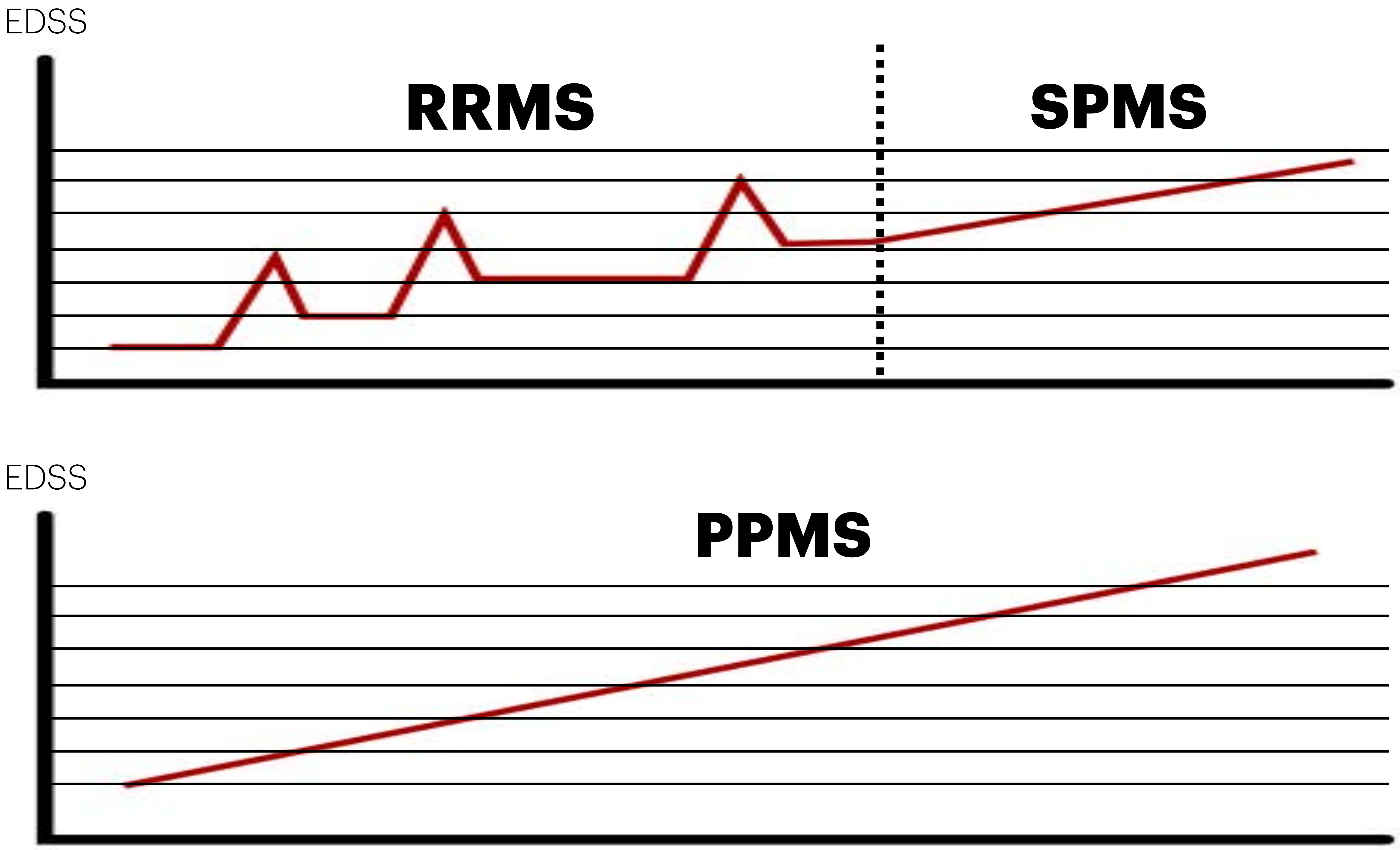
John Kurtzke



Developed two fundamental scales for MS progression

1955: Disability Status Scale (DSS)

1983: Expanded Disability Status Scale (EDSS)


EDSS
RRMS
SPMS
EDSS
PPMS

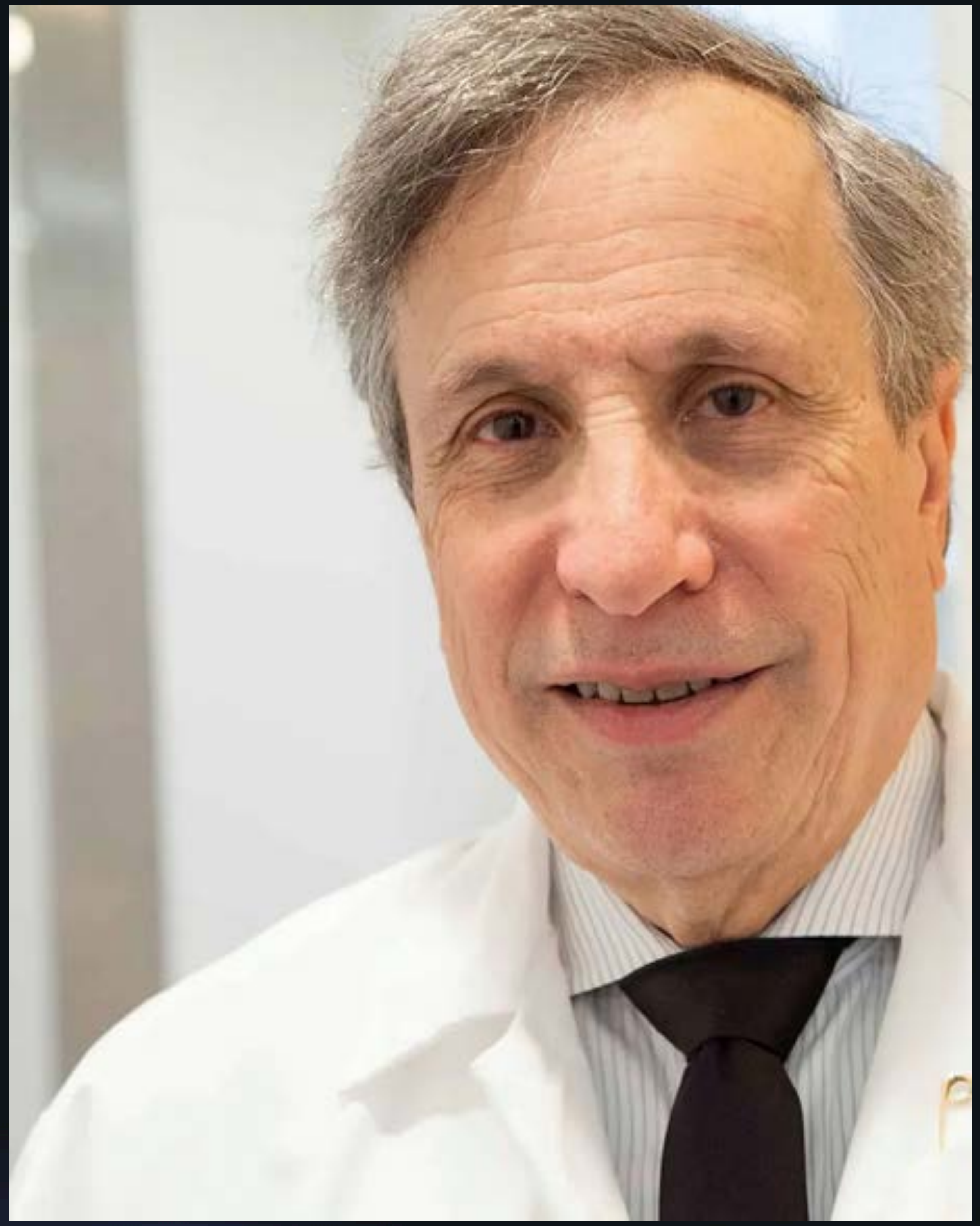
1993

1993 (1995 in EU): Betaseron (Interferon beta-1b):
First disease modifying treatment (DMT) of MS

Soon followed by:

1997: Avonex (Interferon beta-1a)
1998: Rebif (Interferon beta-1a)
1996 (2001 in EU): Copaxone (Glatirameracetat)

1996



Fred Lublin

Standardised and defined the clinical course of multiple sclerosis.

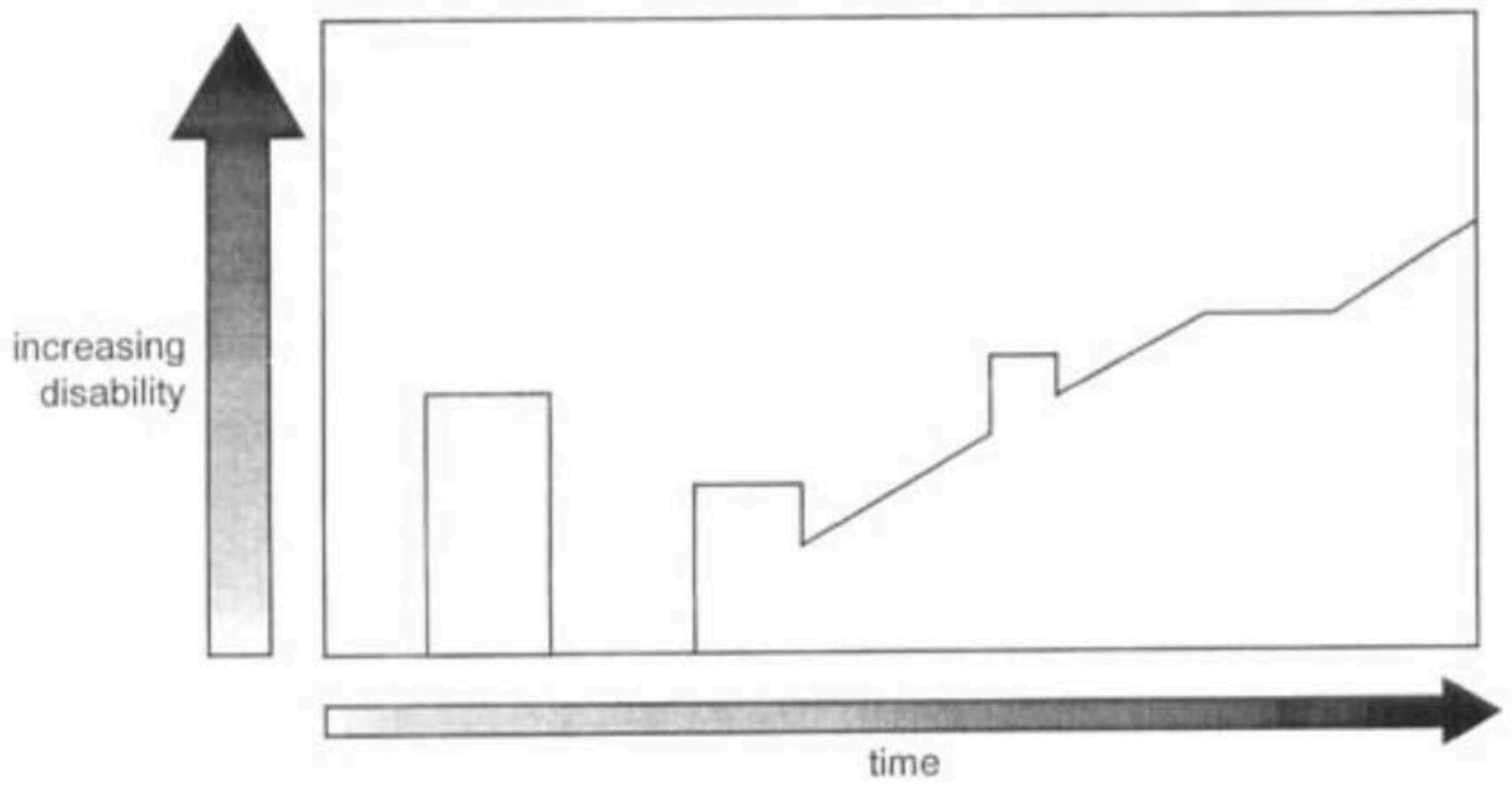
Relapsing Remitting MS (RRMS)
Secondary Progressive MS (SPMS)
Primary Progressive MS (PPMS)

Lublin, F. D., Reingold, S. C. & Sclerosis*, N. M. S. S. (USA) A. C. on C. T. of N. A. in M. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* **46**, 907–911 (1996).

1996

Secondary-progressive (SP) MS. The consensus definition is as follows: initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus (figure 3, a and b).

SP-MS may be seen as a long-term outcome of RR-MS in that most SP patients initially begin with RR disease as defined here. However, once the baseline between relapses begins to progressively worsen, the patient has switched from RR-MS to SP-MS. Eighty-four of 124 respondents chose the above definition.



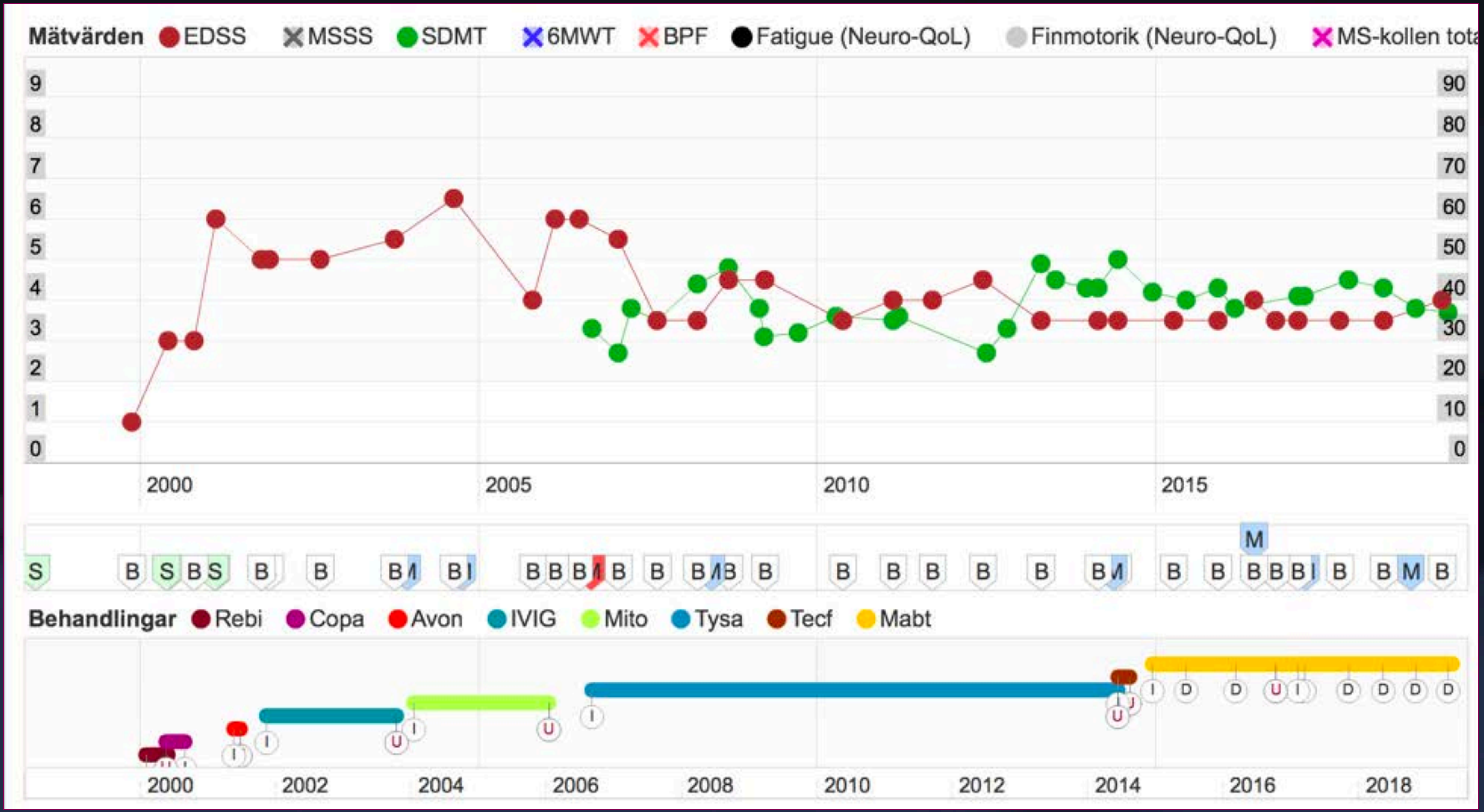
B

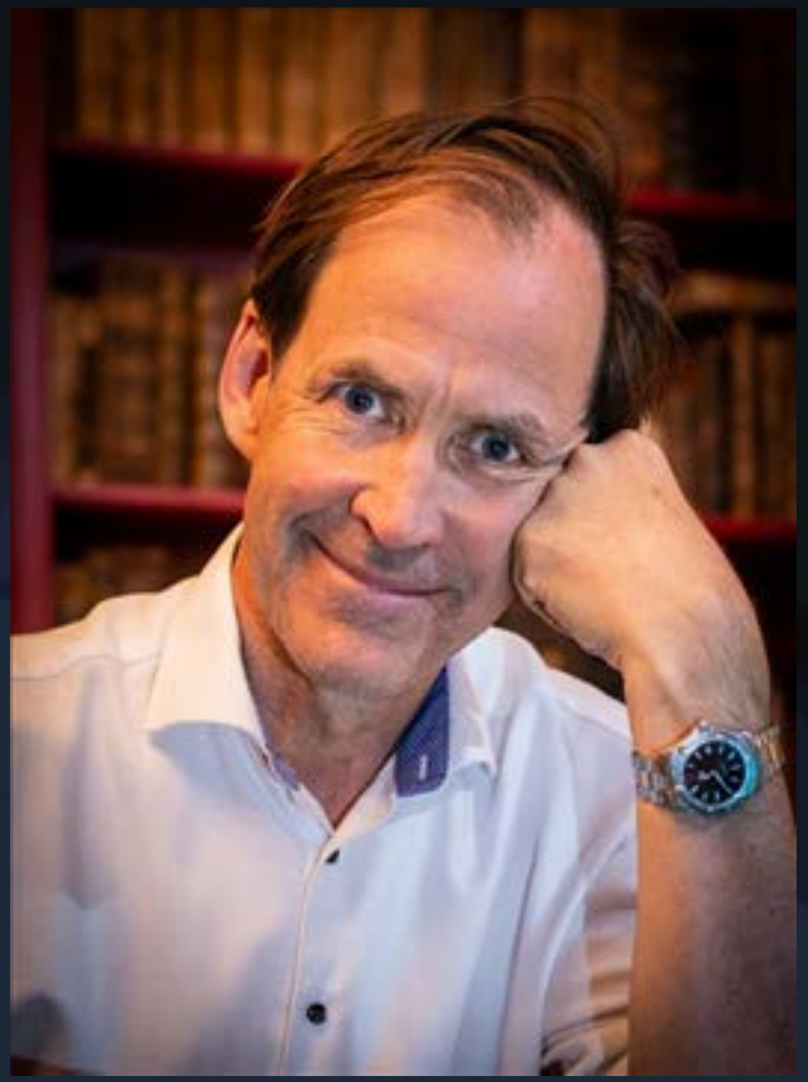
Figure 3. Secondary progressive (SP) MS begins with an initial RR course, followed by progression of variable rate (A) that may also include occasional relapses and minor remissions (B).

Lublin, F. D., Reingold, S. C. & Sclerosis*, N. M. S. S. (USA) A. C. on C. T. of N. A. in M. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* **46**, 907–911 (1996).

2000

The Swedish MS registry officially launched by Jan Hillert





- Coverage N ≈ 24000 patients, > 84%
- Decision tool to enter and visualise data

2004

Tysabri (Natalizumab) from Biogen approved - much stronger effect
Considered second-line use due to risk of rare brain infection:
Progressive Multifocal Leukoencephalopathy (PML)

Considered as high efficacy treatment.

2006

May 2006: First MS patient in Sweden was treated off-label with MabThera by physician Anders Svenningson in Umeå.

Considered as high-efficacy treatment.

2015

Biogen contacted IVO (Health and Social Care Inspectorate) in Sweden, to request "a dialogue" regarding extensive off-label prescription of Rituximab.

IVO opened a supervisory case, closed in 2016, concluding that Rituximab use does not conflict with scientific evidence and proven clinical experience.

It did delay Socialstyrelsen's (National Board of Social Affairs and Health) recommendation on use of Rituximab treatment in MS.

2016-2021: RIFUND

- RIFUND-MS was a multi-centre, phase 3, randomised controlled clinical trial in Sweden, funded by the Swedish Research Council.
- Compared Rituximab (98 patients) vs Dimethyl Fumarate (97 patients), 24-months follow-up
- Primary endpoint: Proportion of patients with at least one relapse
  - 3% of Rituximab patients had a relapse
  - 16% of Dimethyl Fumarate patients had a relapse
- 2022: RIFUND-MS was published in Lancet Neurology
- Used the Swedish MS registry as electronic medical record

Articles

Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial

Anders Svenningsson, Thomas Frisell, Joachim Burman, Jonatan Salzer, Katharina Fink, Susanna Hallberg, Joakim Hambraeus, Markus Axelsson, Faiez Al Nimer, Peter Sundström, Martin Gunnarsson, Rune Johansson, Johan Mellergård, Igal Rosenstein, Ahmad Ayad, Irina Sjöblom, Anette Risedal, Pierre de Flon, Eric Gilland, Jonas Lindeberg, Fadi Shawket, Fredrik Piehl, Jan Lycke

Summary

Background B-cell depleting therapies are highly efficacious in relapsing-remitting multiple sclerosis but one such therapy, rituximab, is not approved for multiple sclerosis and no phase 3 trial data are available. We therefore examined the safety and efficacy of rituximab compared with dimethyl fumarate in patients with relapsing-remitting multiple sclerosis to obtain data that might allow inclusion of rituximab in treatment guidelines.

Methods RIFUND-MS was a multicentre, rater-blinded, active-comparator, phase 3, randomised controlled trial done at 17 Swedish university and community hospitals. Key inclusion criteria for participants were: age 18–50 years; relapsing-remitting multiple sclerosis or clinically isolated syndrome according to prevailing McDonald criteria; 10 years or less since diagnosis; untreated or only exposed to interferons or glatiramer acetate; and with clinical or neuroradiological disease activity in the past year. Patients were automatically randomly assigned (1:1) by the treating physician using a randomisation module in the Swedish multiple sclerosis registry, without stratification, to oral dimethyl fumarate 240 mg twice daily or to intravenous rituximab 1000 mg followed by 500 mg every 6 months. Relapse evaluation, Expanded Disability Status Scale rating, and assessment of MRI scans were done by examining physicians and radiologists masked to treatment allocation. The primary outcome was the proportion of patients with at least one relapse (defined as subacute onset of new or worsening neurological symptoms compatible with multiple sclerosis with a duration of more than 24 h and preceded by at least 30 days of clinical stability), assessed in an intention-to-treat analysis using log-binomial regression with robust standard errors. This trial is registered at ClinicalTrials.gov, NCT02746744.

Findings Between July 1, 2016, and Dec 18, 2018, 322 patients were screened for eligibility, 200 of whom were randomly assigned to a treatment group (100 assigned to rituximab and 100 assigned to dimethyl fumarate). The last patient completed 24-month follow-up on April 21, 2021. 98 patients in the rituximab group and 97 patients in the dimethyl fumarate group were eligible for the primary outcome analysis. Three (3%) patients in the rituximab group and 16 (16%) patients in the dimethyl fumarate group had a protocol-defined relapse during the trial, corresponding to a risk ratio of 0·19 (95% CI 0·06–0·62; p=0·0060). Infusion reactions (105 events [40·9 per 100 patient-years]) in the rituximab group and gastrointestinal reactions (65 events [47·4 per 100 patient-years]) and flush (65 events [47·4 per 100 patient-years]) in the dimethyl fumarate group were the most prevalent adverse events. There were no safety concerns.

Interpretation RIFUND-MS provides evidence that rituximab given as 1000 mg followed by 500 mg every 6 months is superior to dimethyl fumarate in preventing relapses over 24 months in patients with early relapsing-remitting multiple sclerosis. Health economic and long-term safety studies of rituximab in patients with multiple sclerosis are needed.

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See Comment page 672

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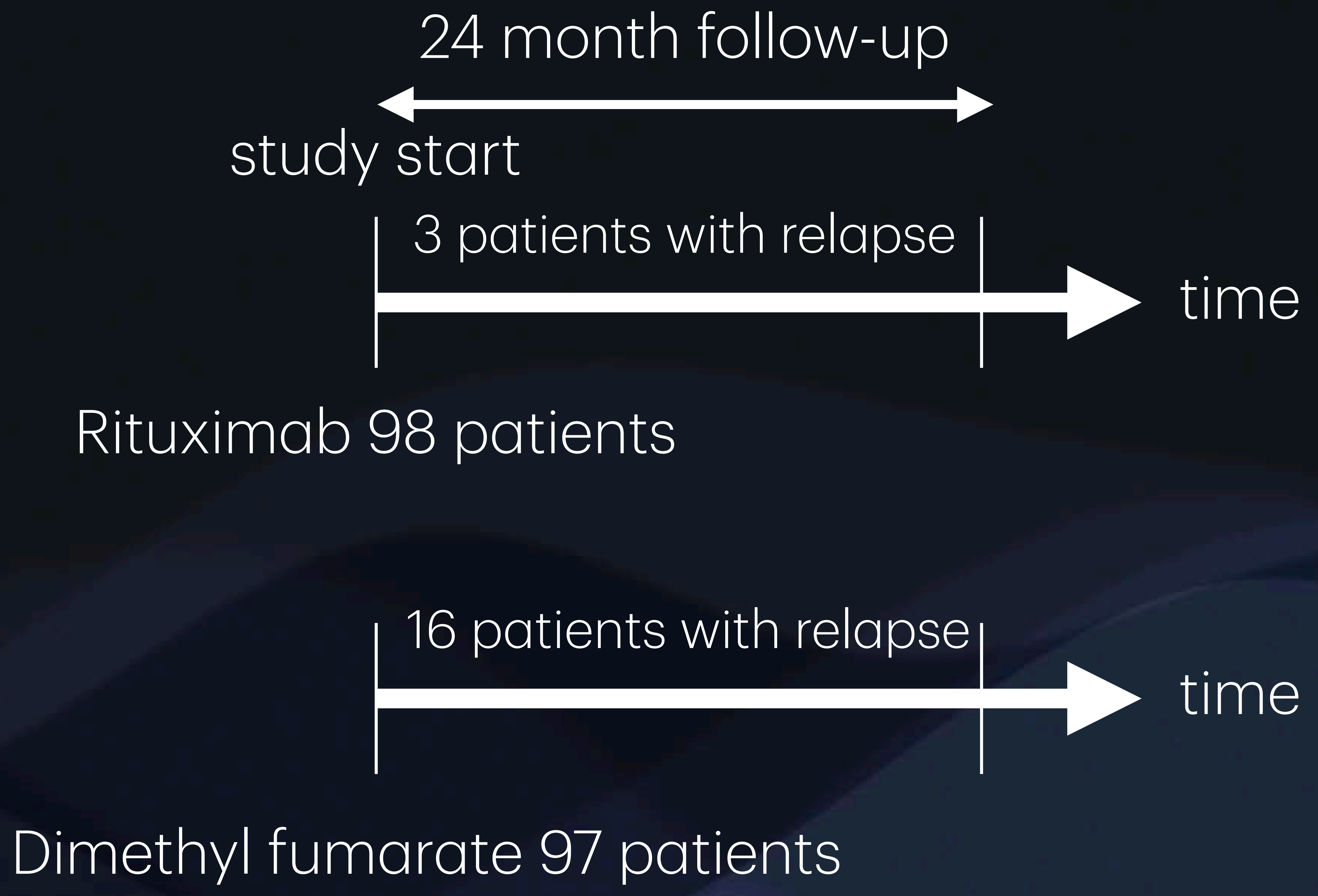
Introduction

The efficacy of rituximab, an anti-CD20 B-cell depleting monoclonal antibody, in preventing inflammatory disease activity in relapsing-remitting multiple sclerosis was first shown in the phase 2 HERMES trial, with a 91% reduction in contrast-enhancing MRI lesions and a halved rate of clinical relapses compared with placebo over 48 weeks.[1] Despite these encouraging data, clinical development of rituximab for multiple sclerosis was paused, and was instead continued with ocrelizumab, a humanised anti-CD20 B-cell depleting monoclonal antibody, in a phase 3 trial.[2] Therefore, rituximab does not have formal approval for treatment of relapsing-remitting multiple sclerosis.

2016-2021: RIFUND



2018

Rituximab share of new MS treatment reached 53.5% in Sweden

2018

Ocrevus (Ocrelizumab) from Genetech (Roche).
Anti-CD20 treatment, comparable with Rituximab.
A humanised antibody (90%), with slightly lower risk of infections compared to Rituximab.

Some treatments

Year	Treatment	Efficacy
1993 (1995)	Betaferon	Low
1997	Avonex	Low
1998	Rebif	Low
1996 (2001)	Copaxone	Low
1998 (2006)	MabThera	Very high
2004	Tysabri	High
2011	Gilenya	High
2013	Lemtrada	Very high
2014	Tecfidera	Moderate
2018	Ocrevus	Very high
2019	Cladribine	High
2021	Kesimpta	Very high

RTX vs OCR

Annual cost of treatment:

Ocrevus treatment cost: 205000 SEK ≈ 18500 Euro
Rituximab treatment cost: 17500 SEK ≈ 1600 Euro

More-EUROPA MS case study

- Study 1-2 (Elena Mouresan): Target trial emulation of RIFUND using data from Swedish MS registry (after removing RIFUND patients)
- Study 3 (Bo Bekkouche): Meta-analysis comparing Rituximab, Ocrelizumab, and Dimethyl Fumarate in four MS-registries in Europe. Sweden (SMSR), Denmark (DMSR), Czech Republic (ReMuS), Italy (IMSR)
- Study 4 (Lars Forsberg): Developing federated learning methods for comparing Rituximab, Ocrelizumab, and Dimethyl Fumarate in Europe as if data was pooled.

Study 4 example (step 1)

- Two study arms, three registries (Sweden (SMSR), Denmark (DMSR), Czech Republic (ReMuS)):
  - Study arm 1: Rituximab + Ocrelizumab = Anti-CD20 study arm
  - Study arm 2: Dimethyl Fumarate
- Inclusion criteria: age 18-60, EDSS ≤ 5.5, start of treatment 2014 -2021
- Logistic regression model to calculate Propensity Score and weights:
  - logit(P(arm1)) ~ intercept + age + sex + timetoindex + prevrelapse + prevrelapse*DMSR + prevrelapse*ReMuS + prevlreapse*IMSR + DMSR + ReMuS + IMSR
  - Inverse Probability of Treatment Weights (IPTW)

$$w_i = \begin{cases} \frac{1}{e(x_i)} & \text{if arm1}_i = 1 \\ \frac{1}{1 - e(x_i)} & \text{if arm1}_i = 0 \end{cases}$$

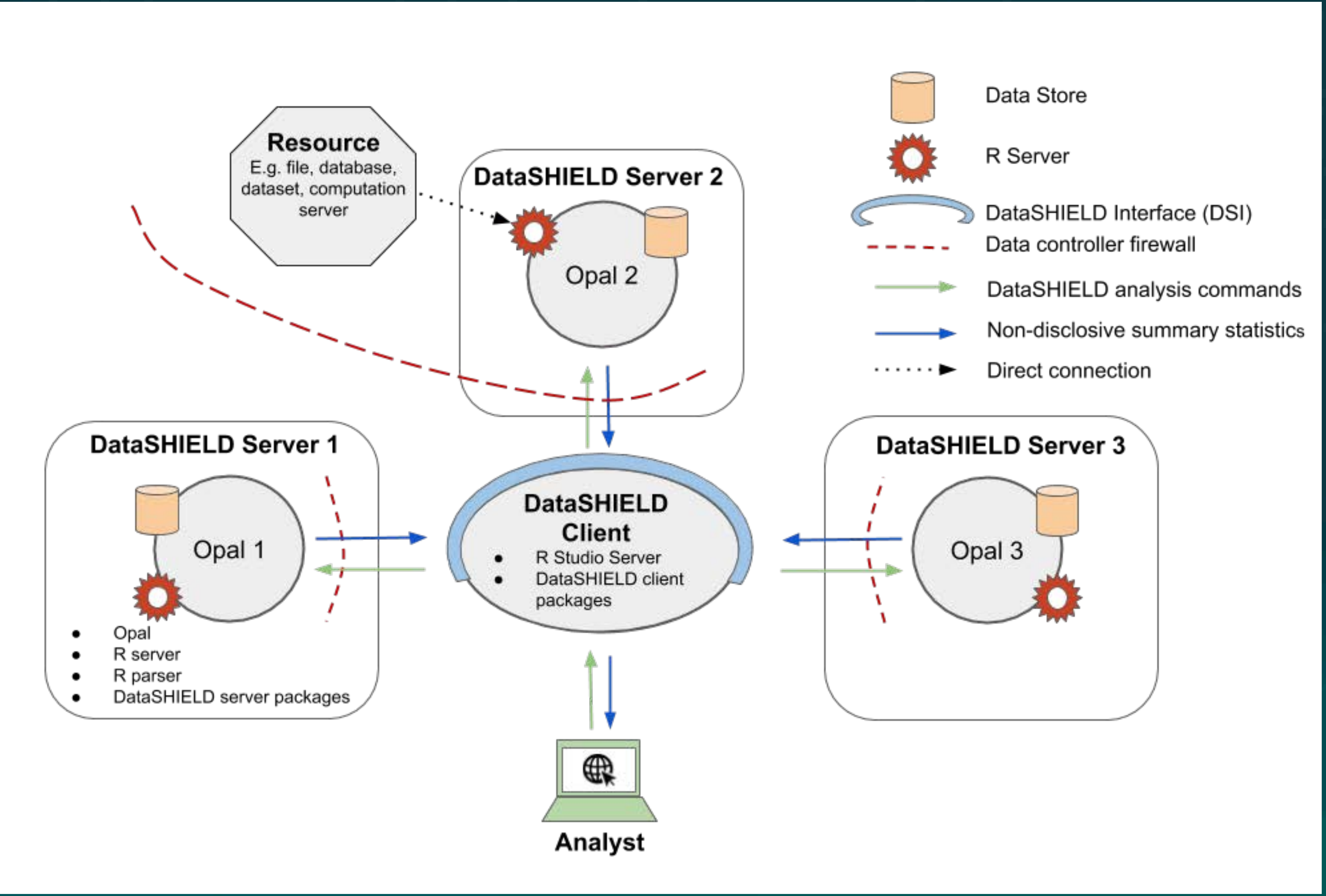
- Once PS model is settled: Run log-binomial test on difference in relapse activity between the two arms during 24 month follow-up by applying weights

Federated learning: How can we run the analysis if we cannot merge data?

- Meta analysis
- Bayesian approach
- Artificial Intelligence model of synthetic patients
- **Federated learning through Distributed computing**
  - **Mathematically identical to running it merged!**

Federated Learning

DataSHIELD

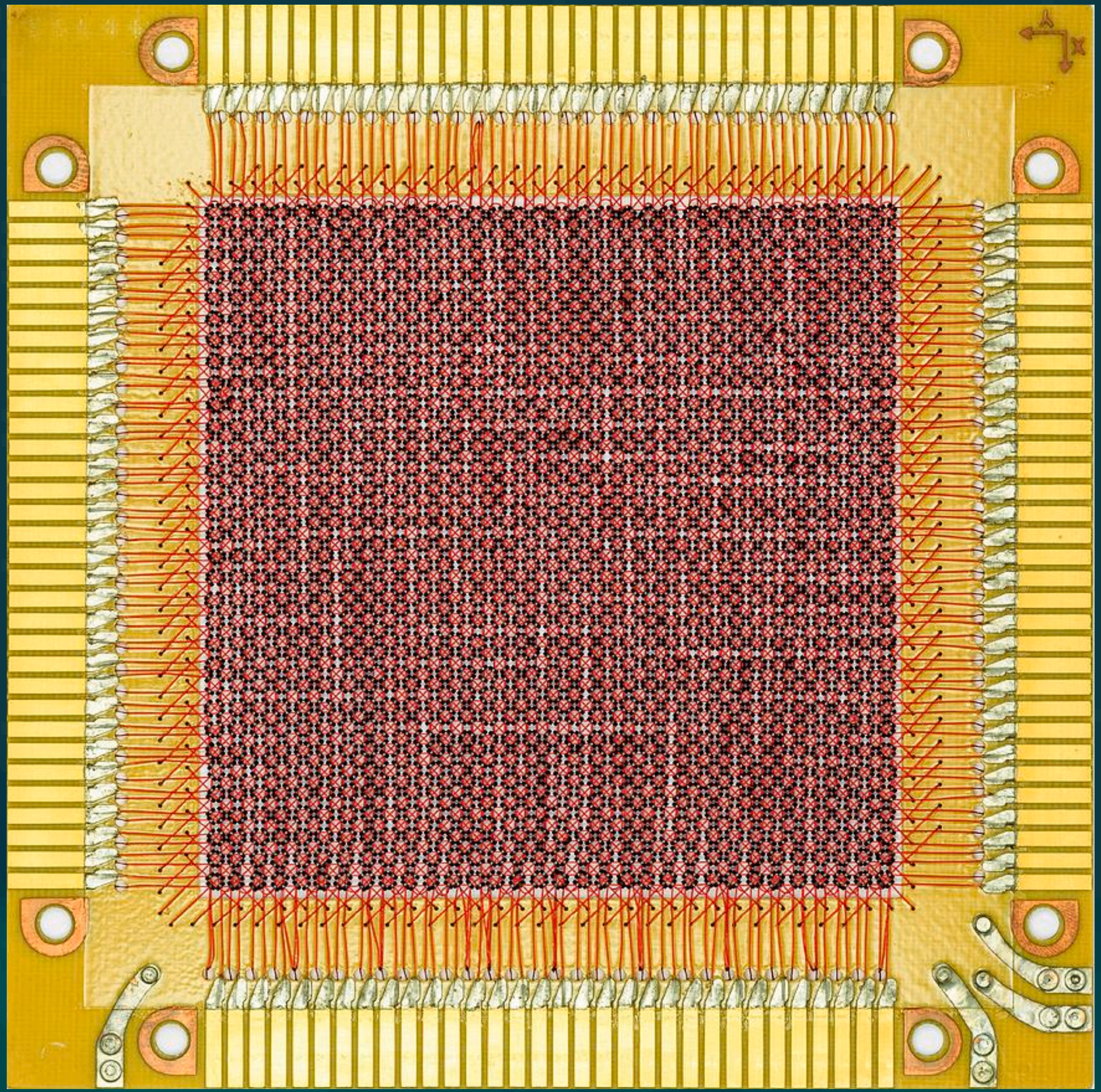


The idea of "FedMeshify":

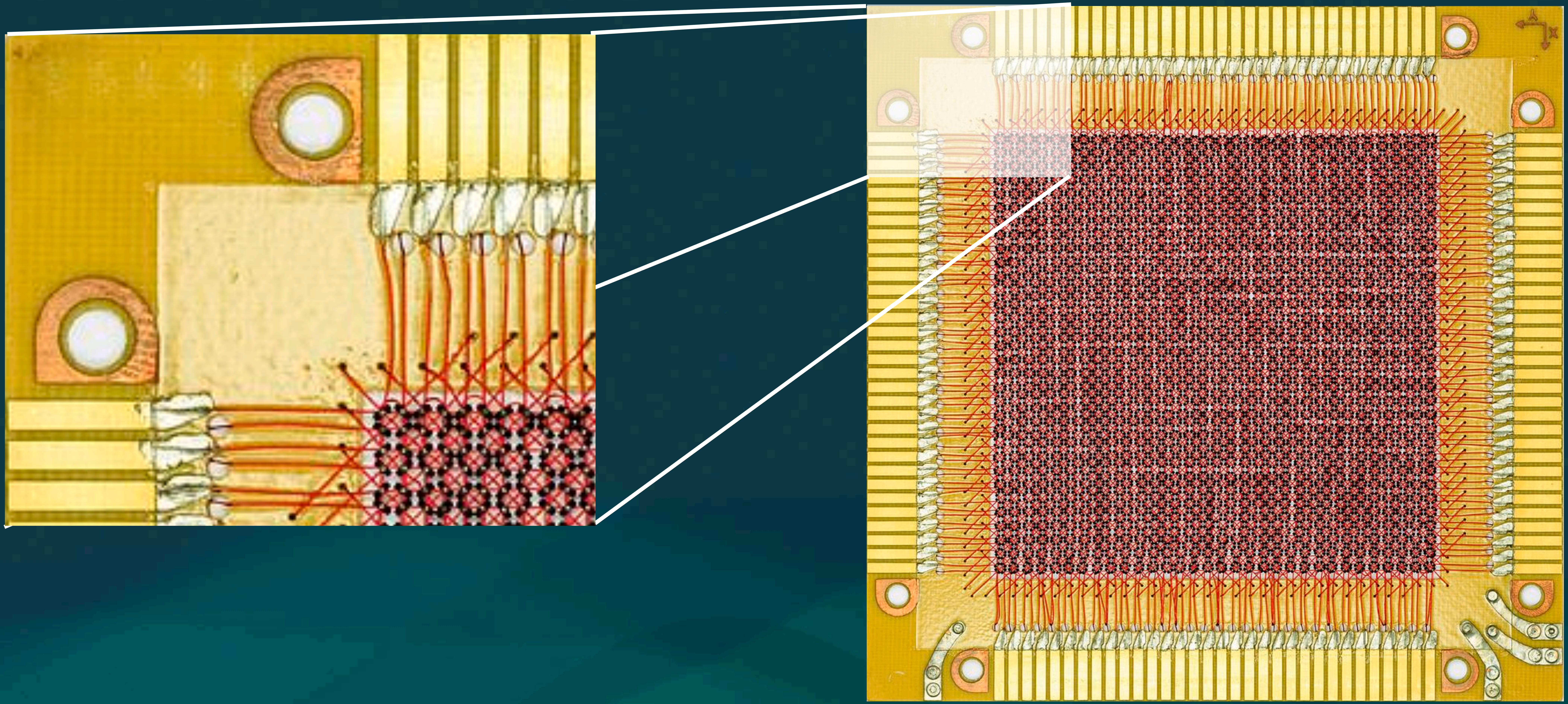
- Make it simple to run: Only one R-script and an internet connection at each site
- One R-script for running the model
- Communicate through existing file distribution services
- We need a CDM.
- Case example: Logistic regression

How are data stored when pooled?

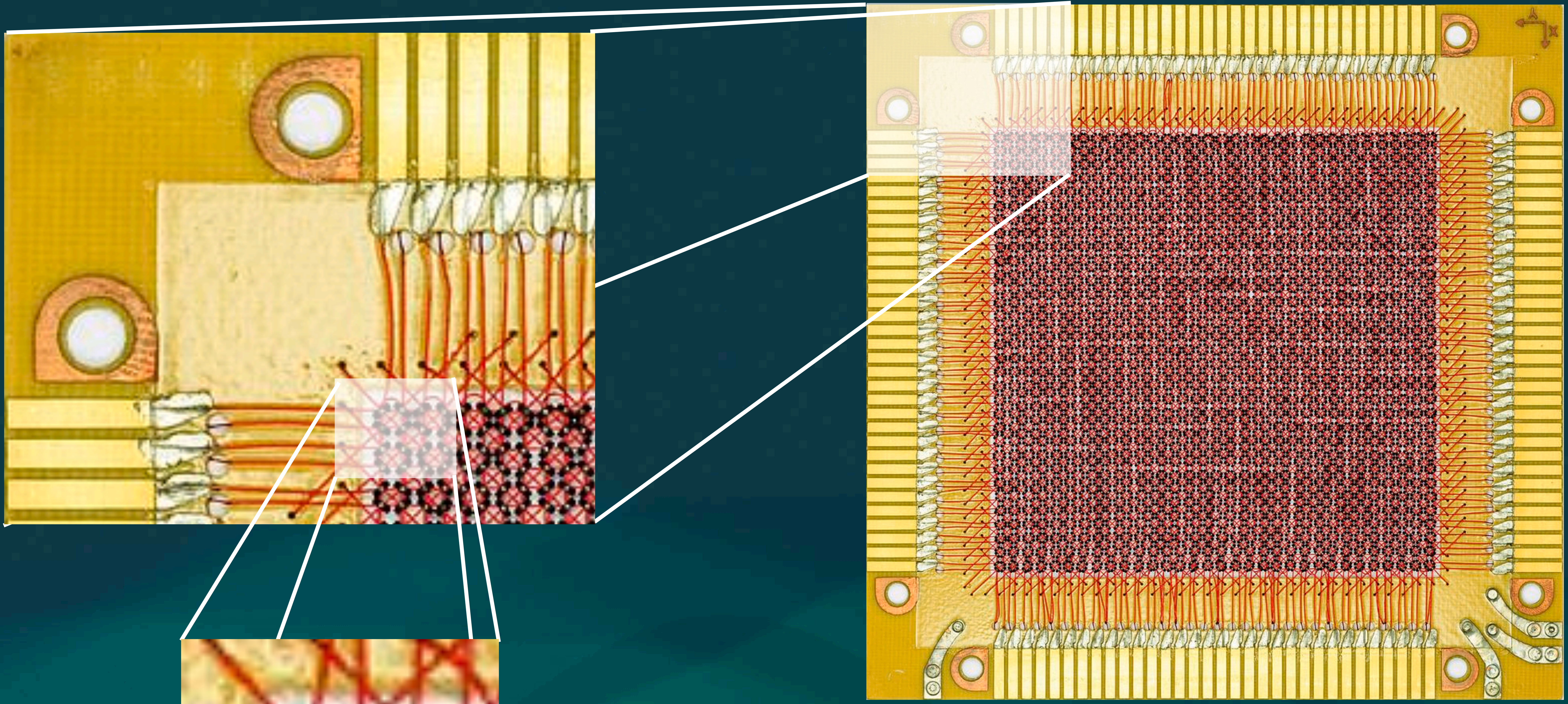
UNIVAC computer from 1961!



Core memory

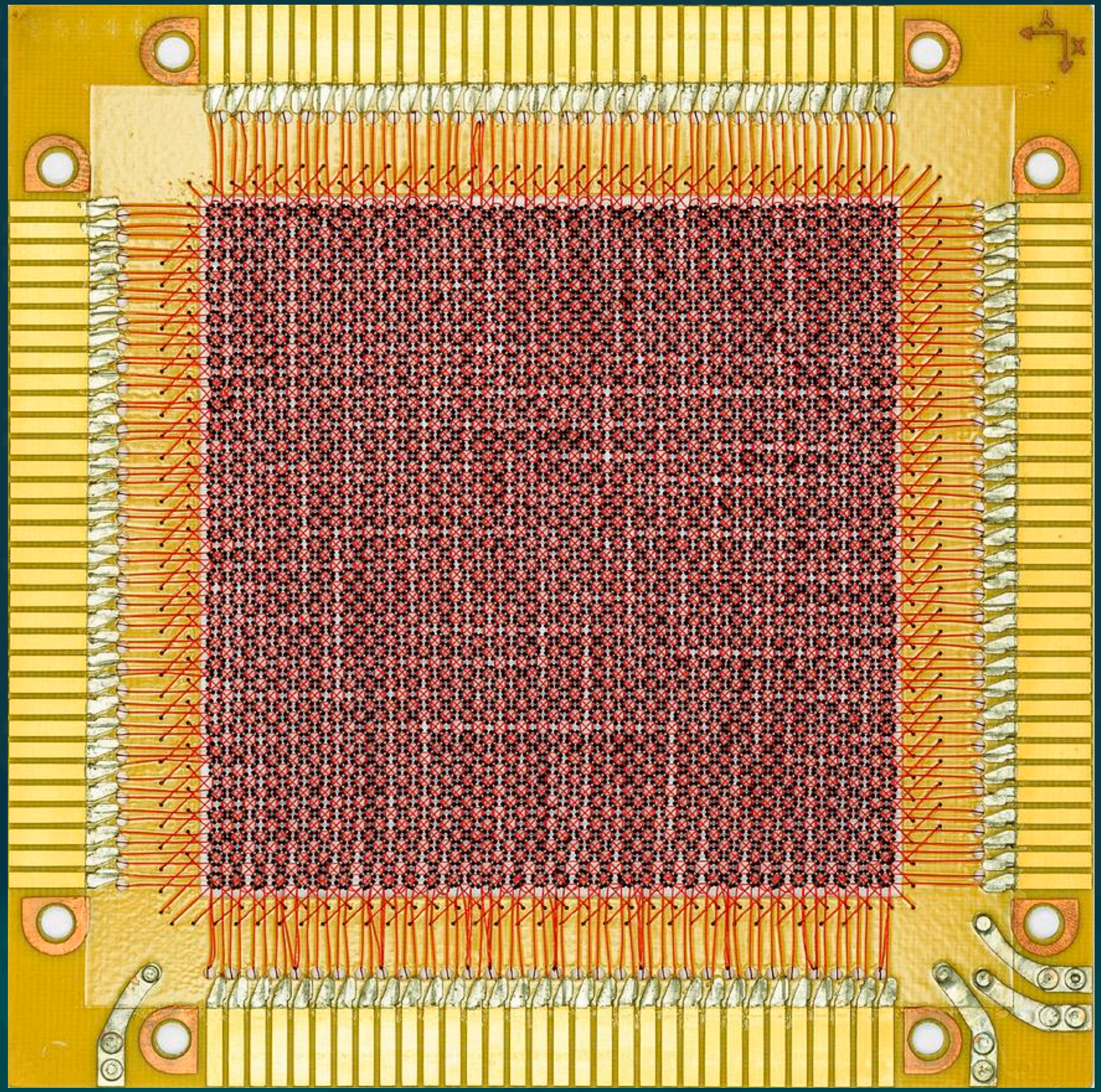


Core memory

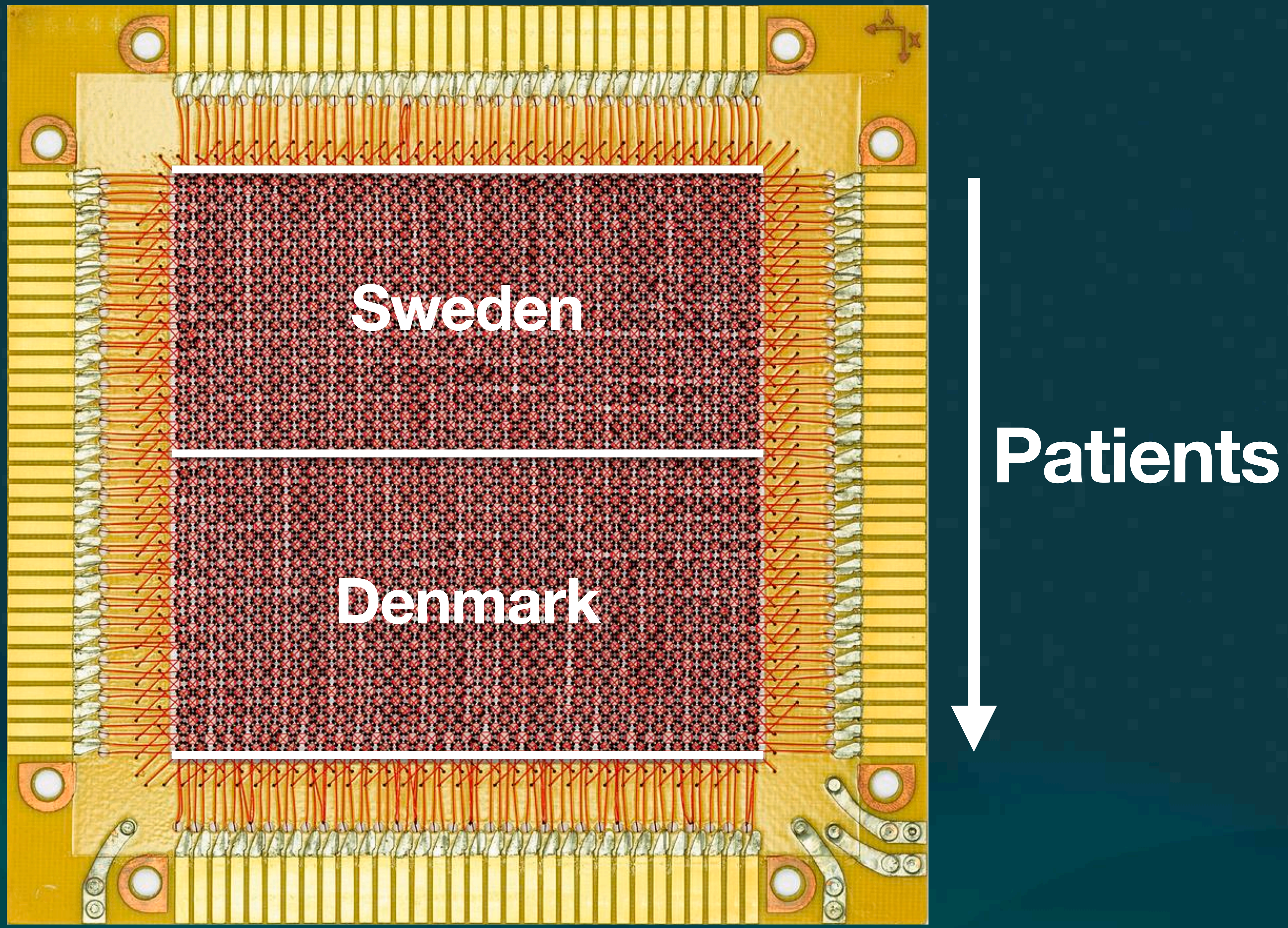


Core memory

- 32x32 = 1024 bits = 128 bytes

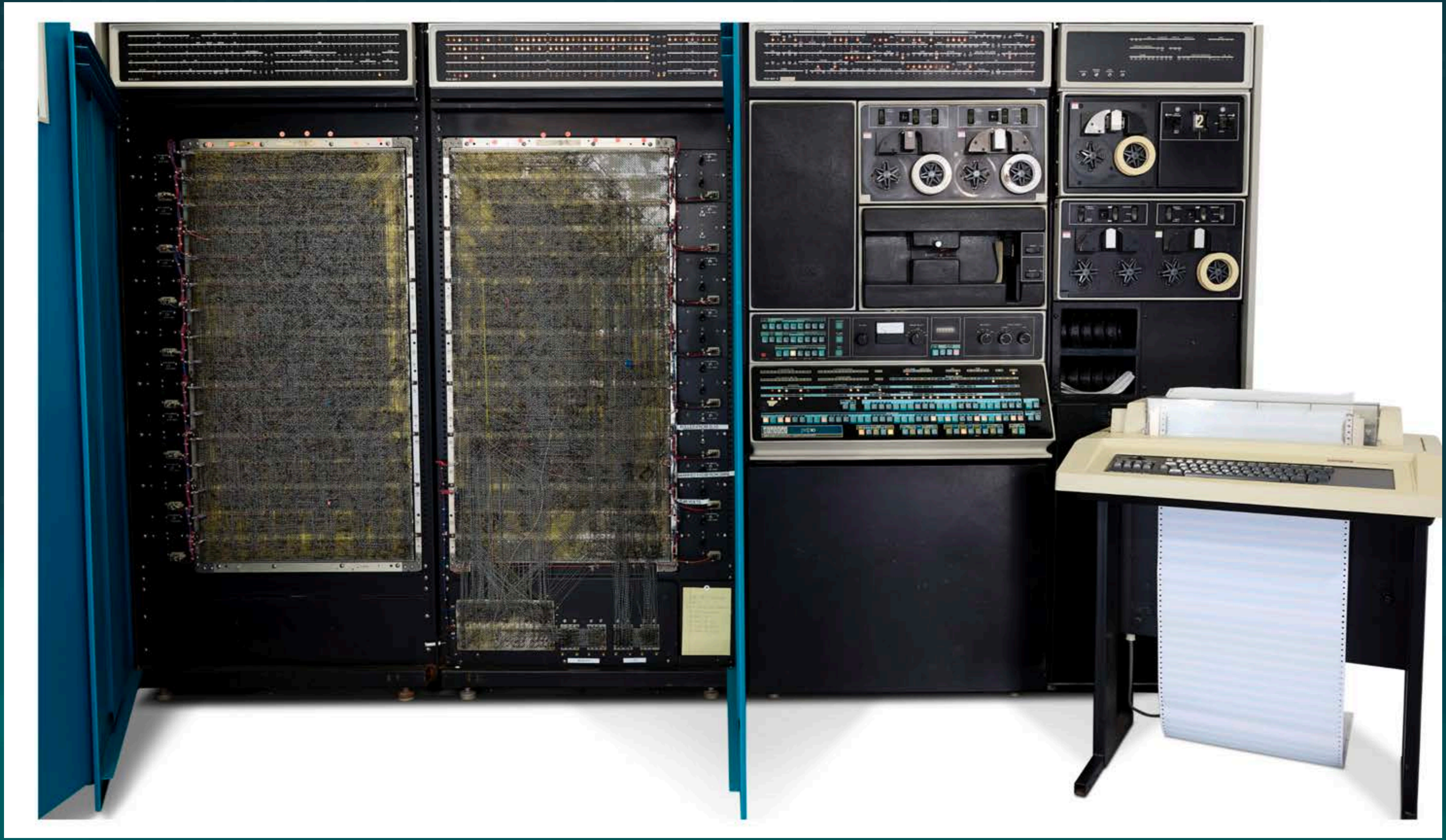


- 32x32 = 1024 bits = 128 bytes
- Assume data from two registries: 64 bytes each = 64 patients:
  - Age 5 bits (e.g. age 30-61)
  - Sex 1 bits
  - Disease course 1 bits
  - Country 1 bits

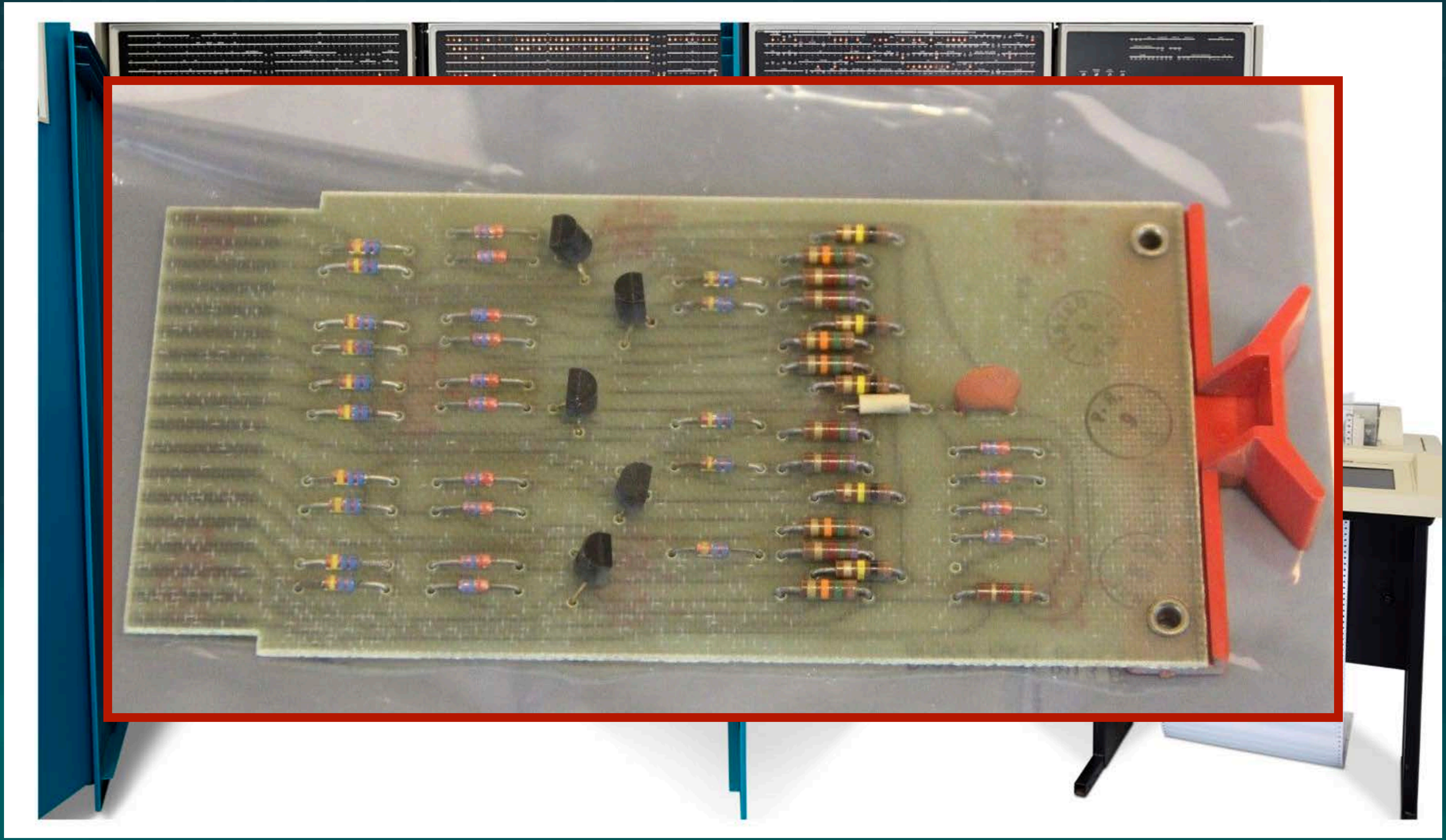


But how does it compute!?

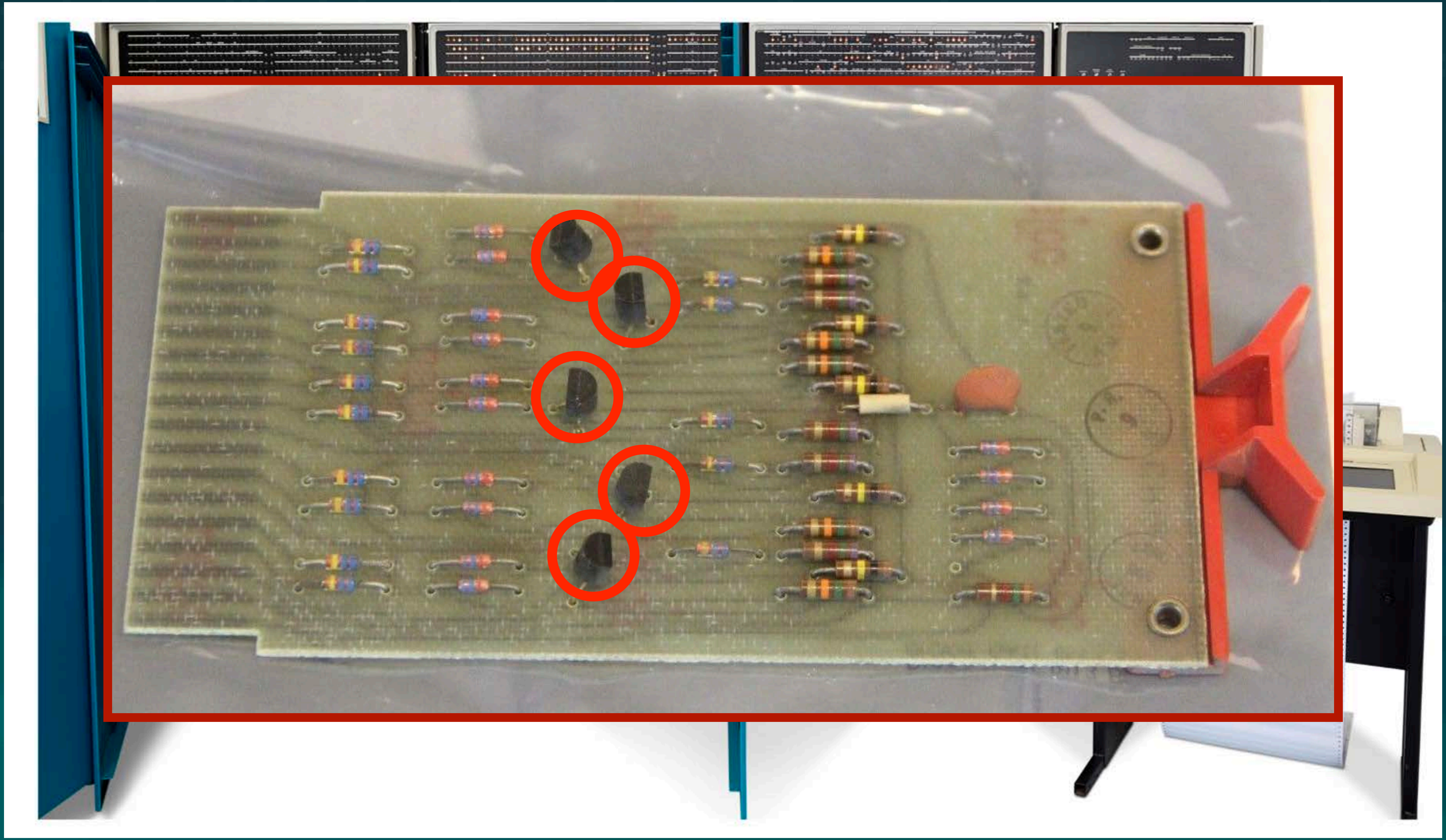
Digital Equipment DEC-10



1966

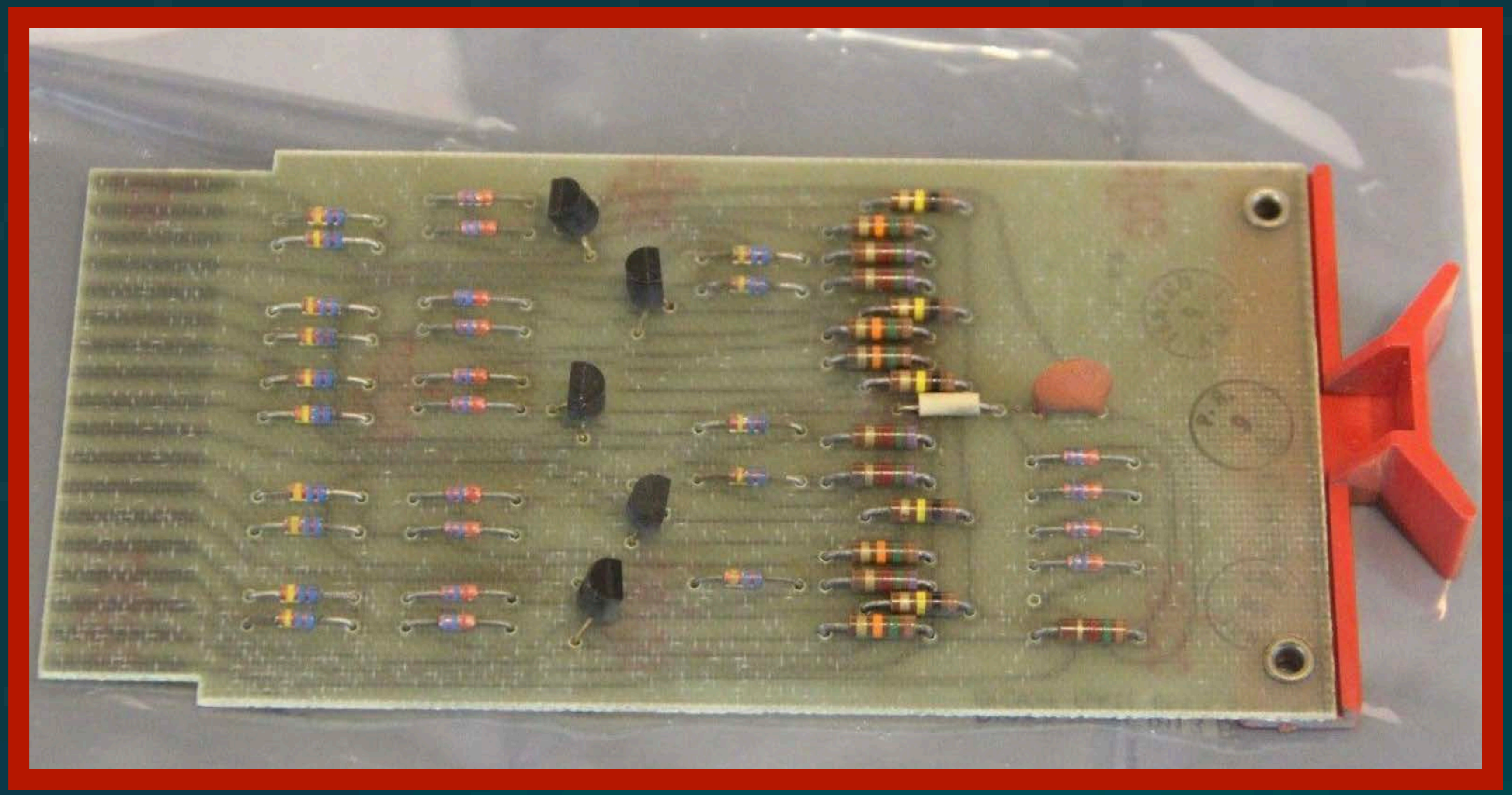


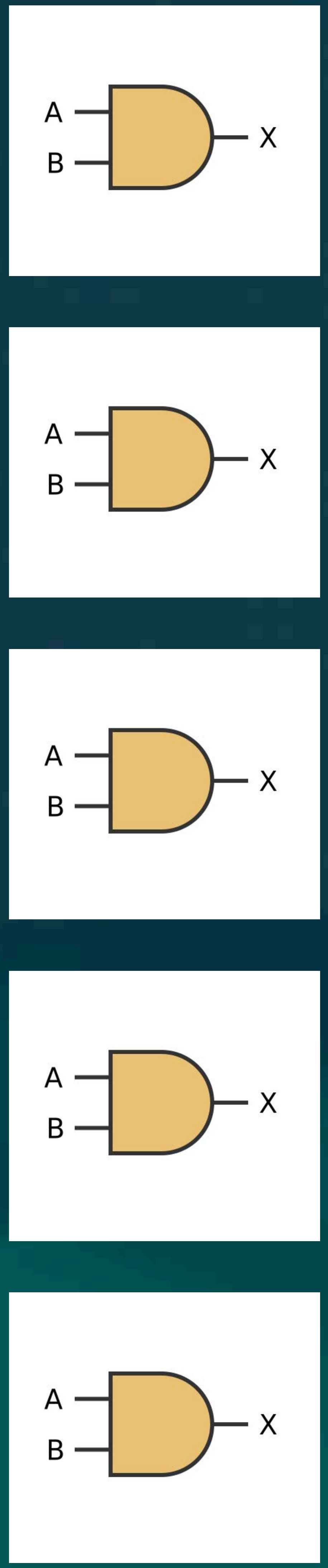
1966

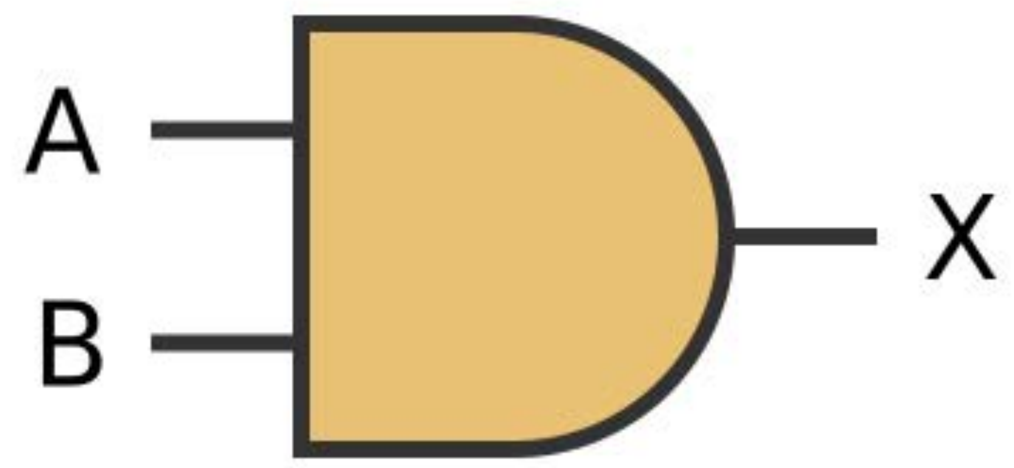


1966

Five boolean AND in parallel!



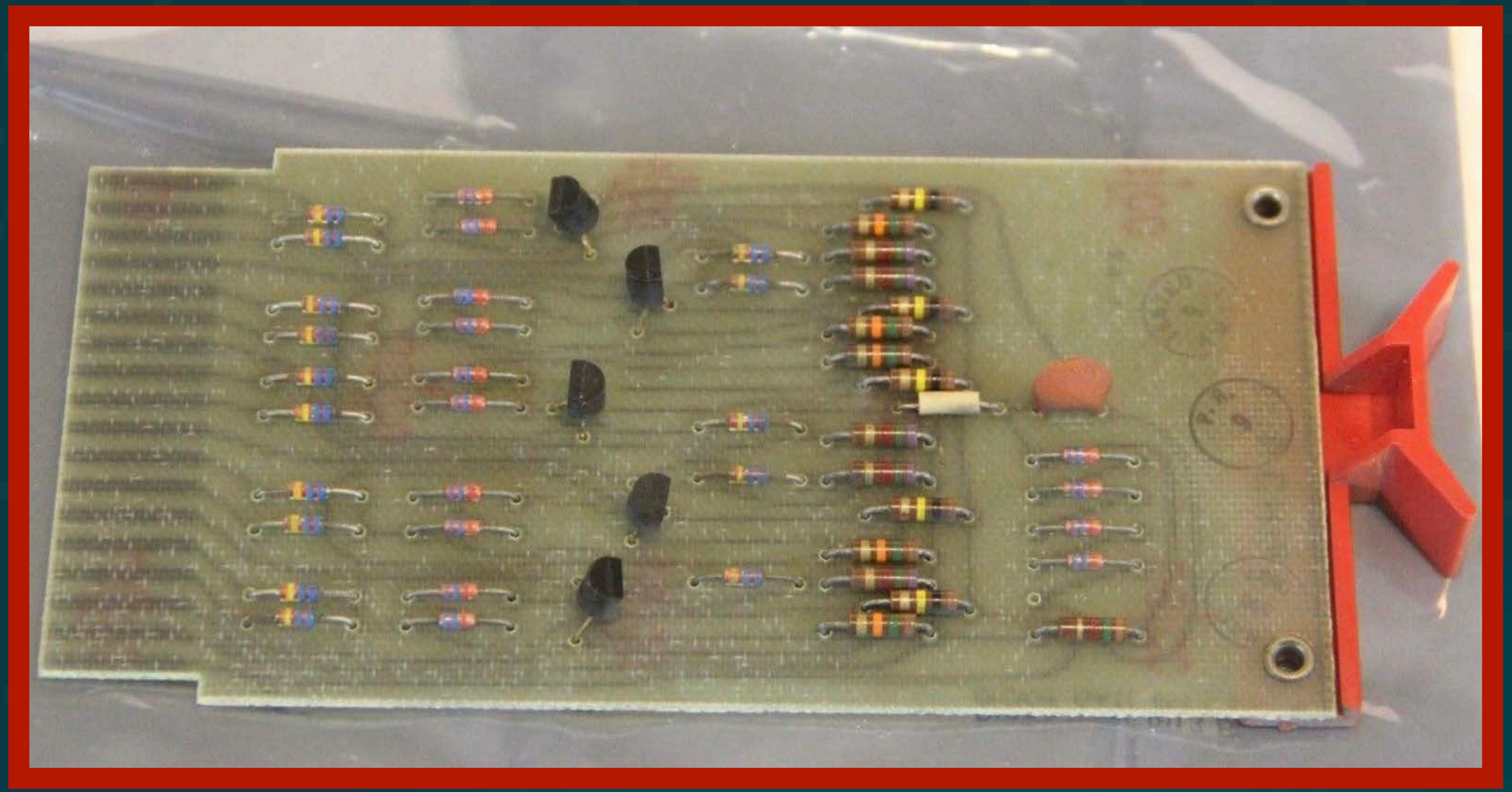


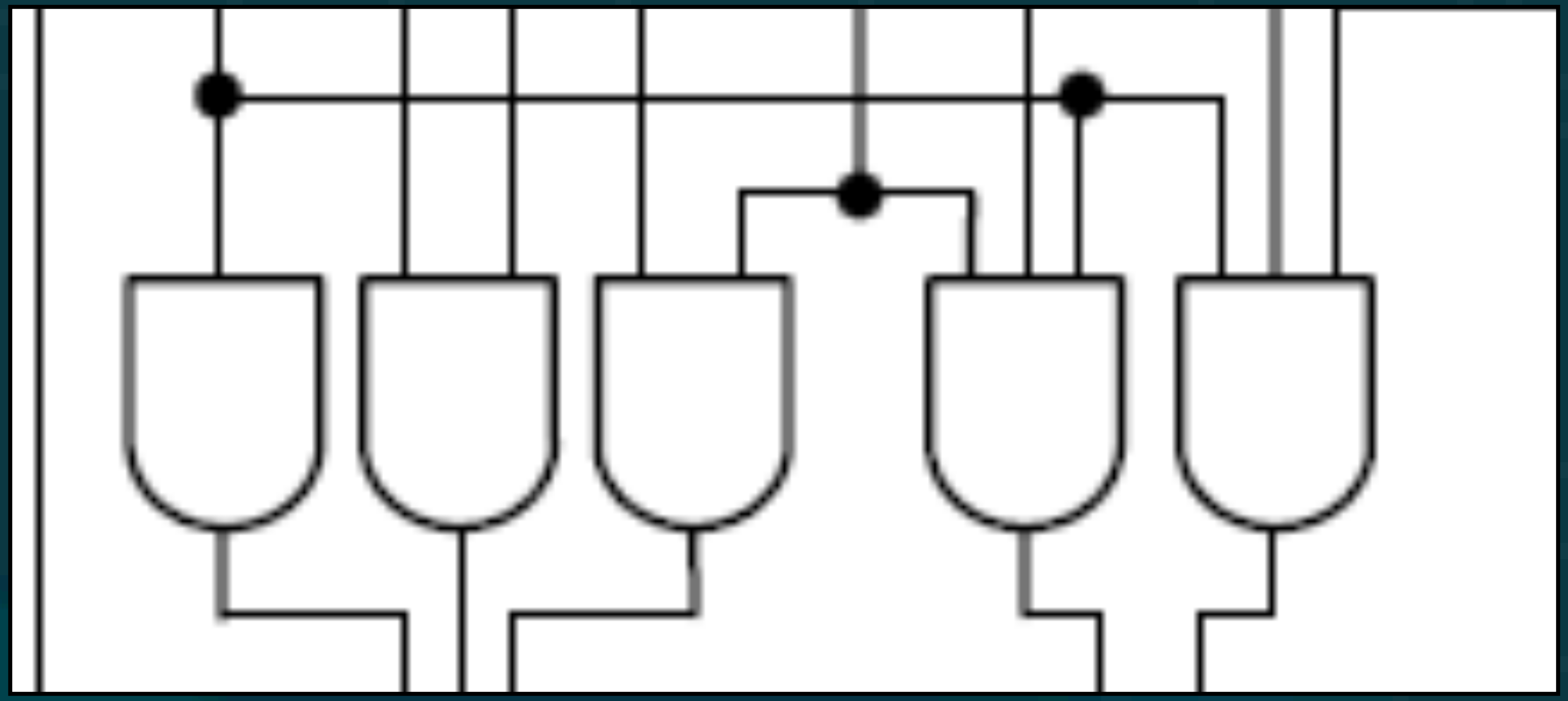


A	B	X
0	0	0
0	1	0
1	0	0
1	1	1

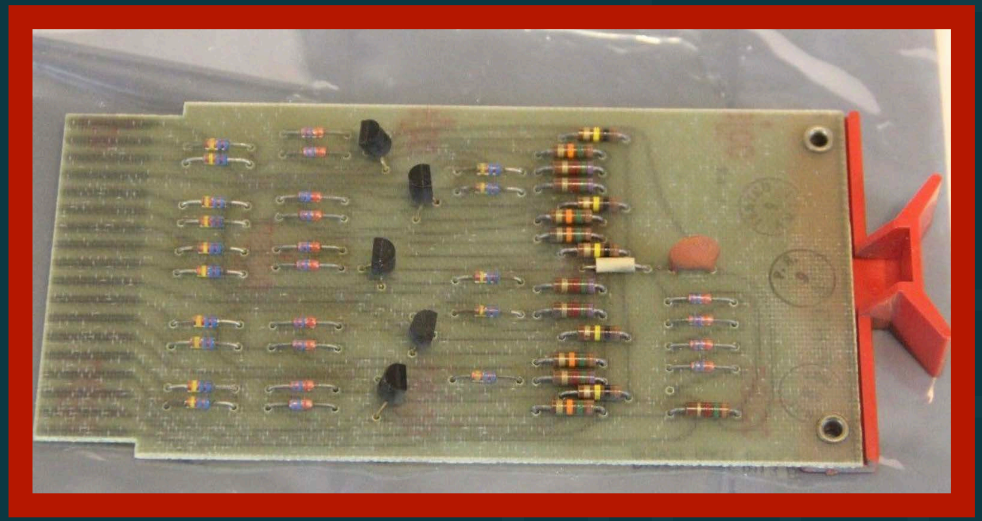
1966

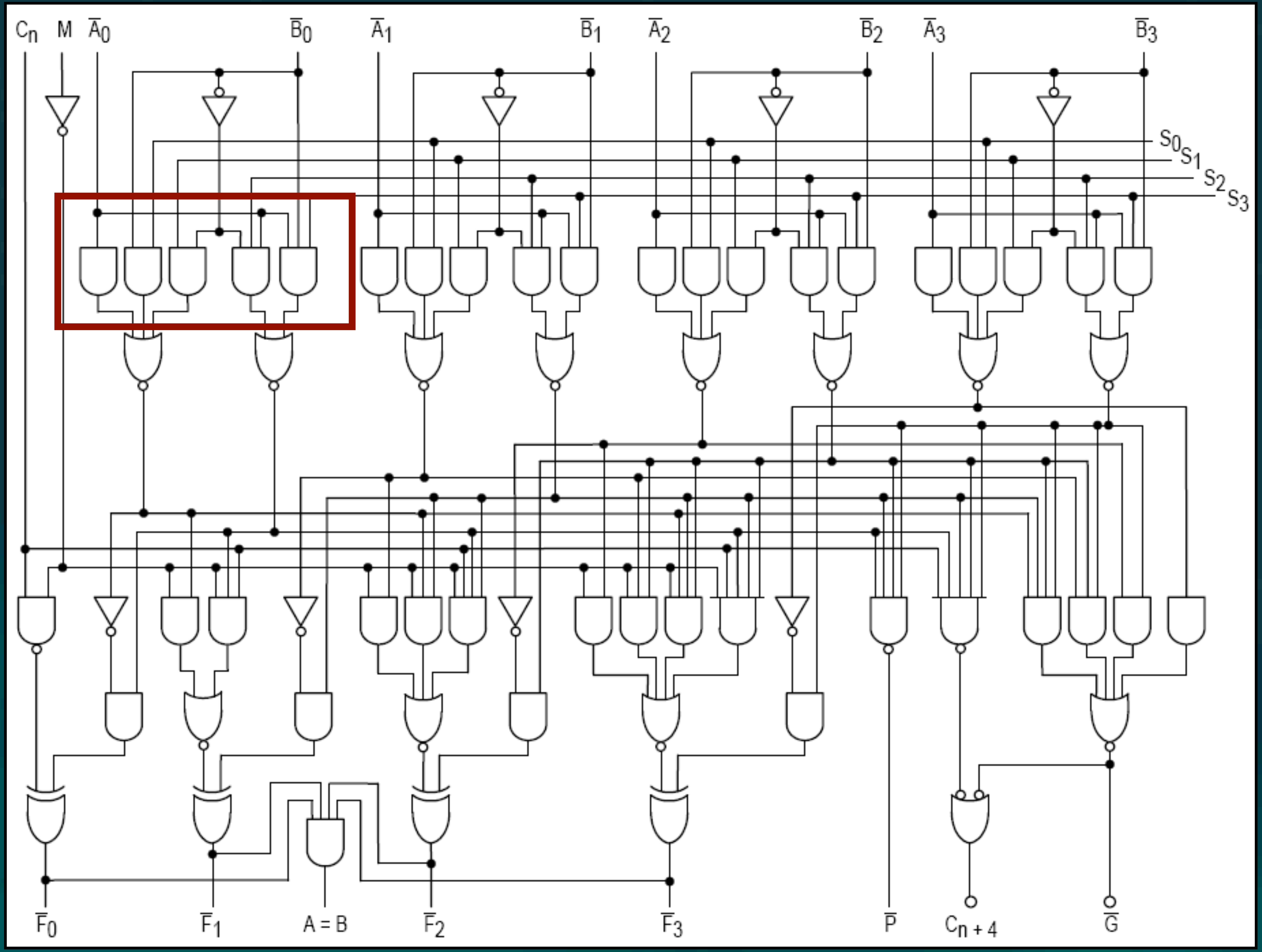
Five boolean AND in parallel!





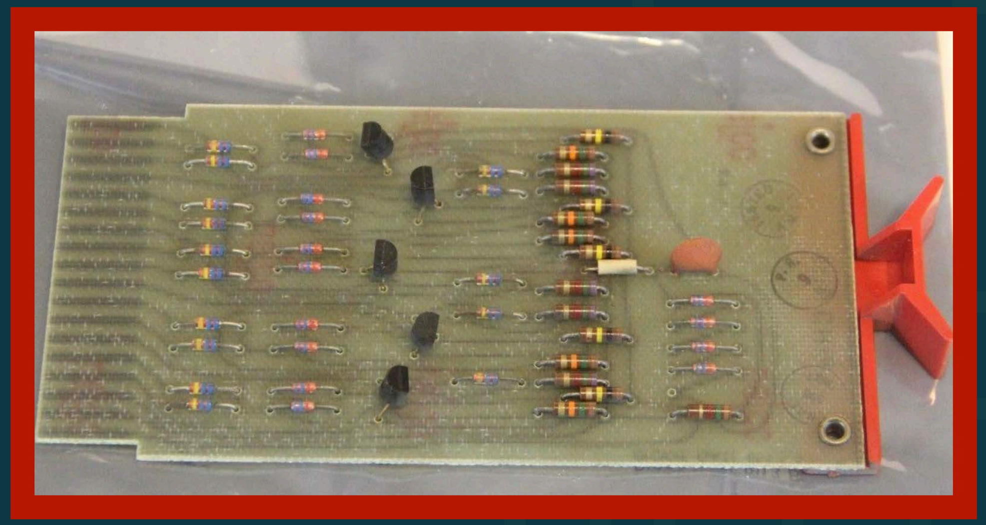
Computing is inherently parallel!

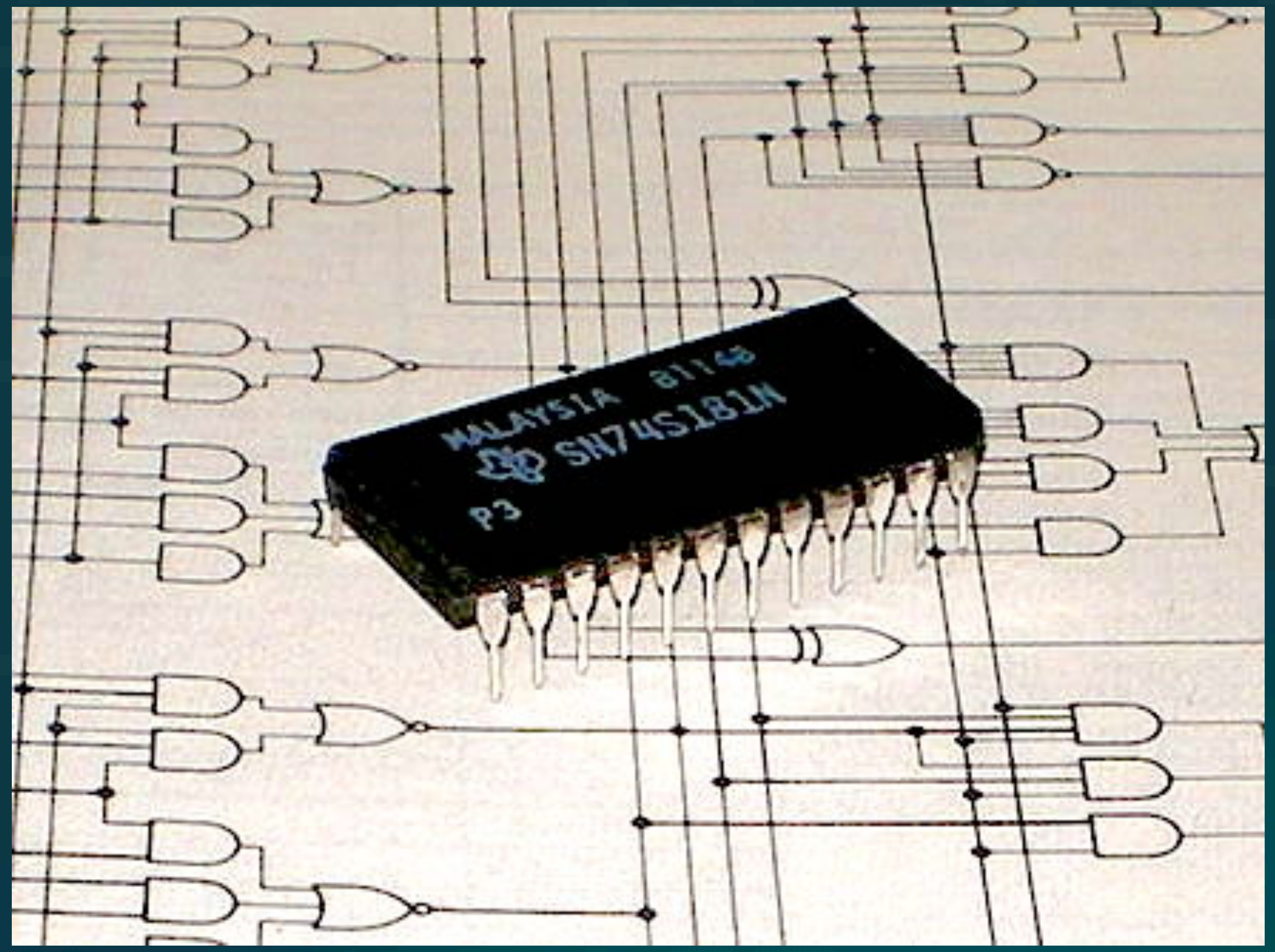


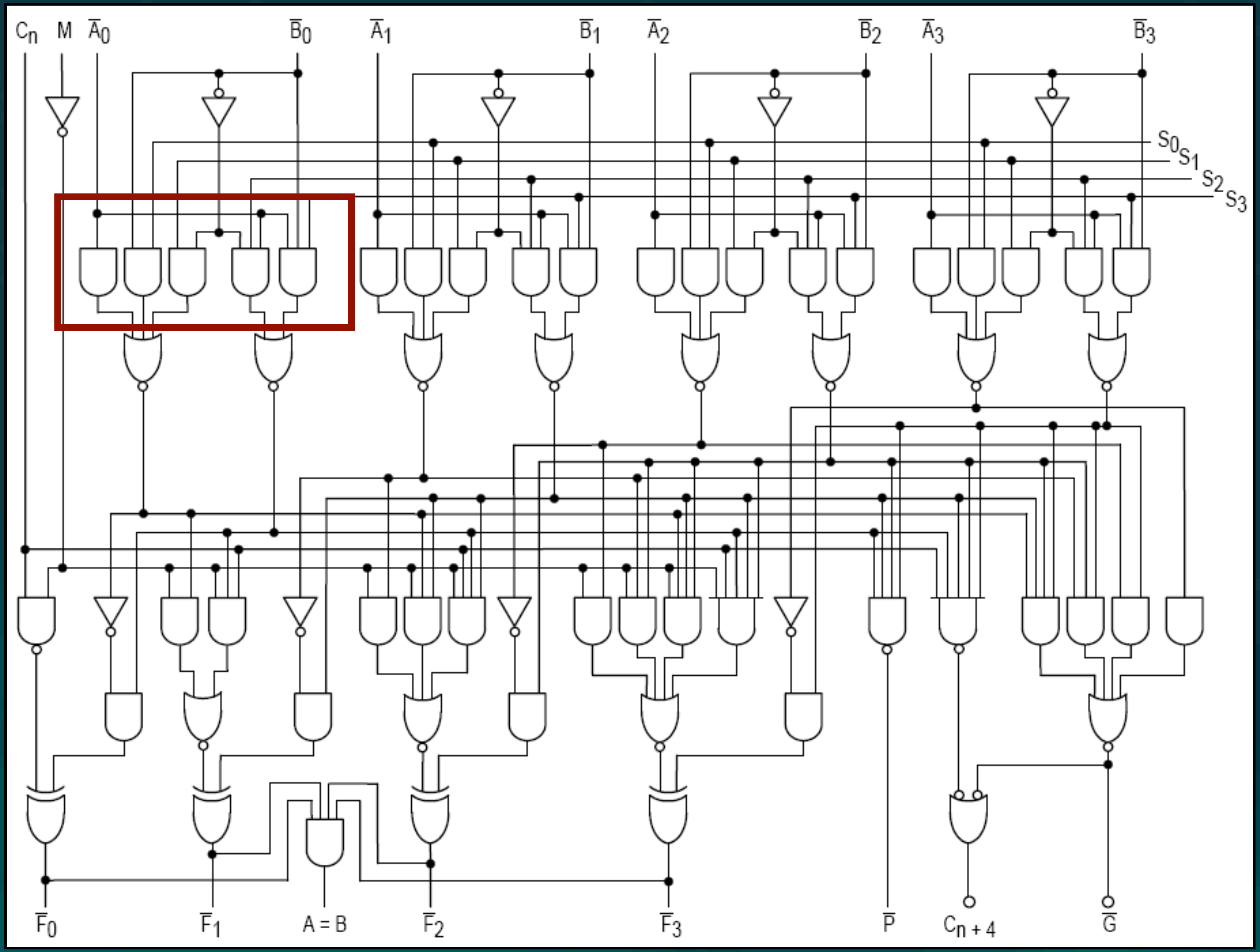


74181 Arithmetic Logic Unit (ALU) 1969

Computing is inherently parallel!

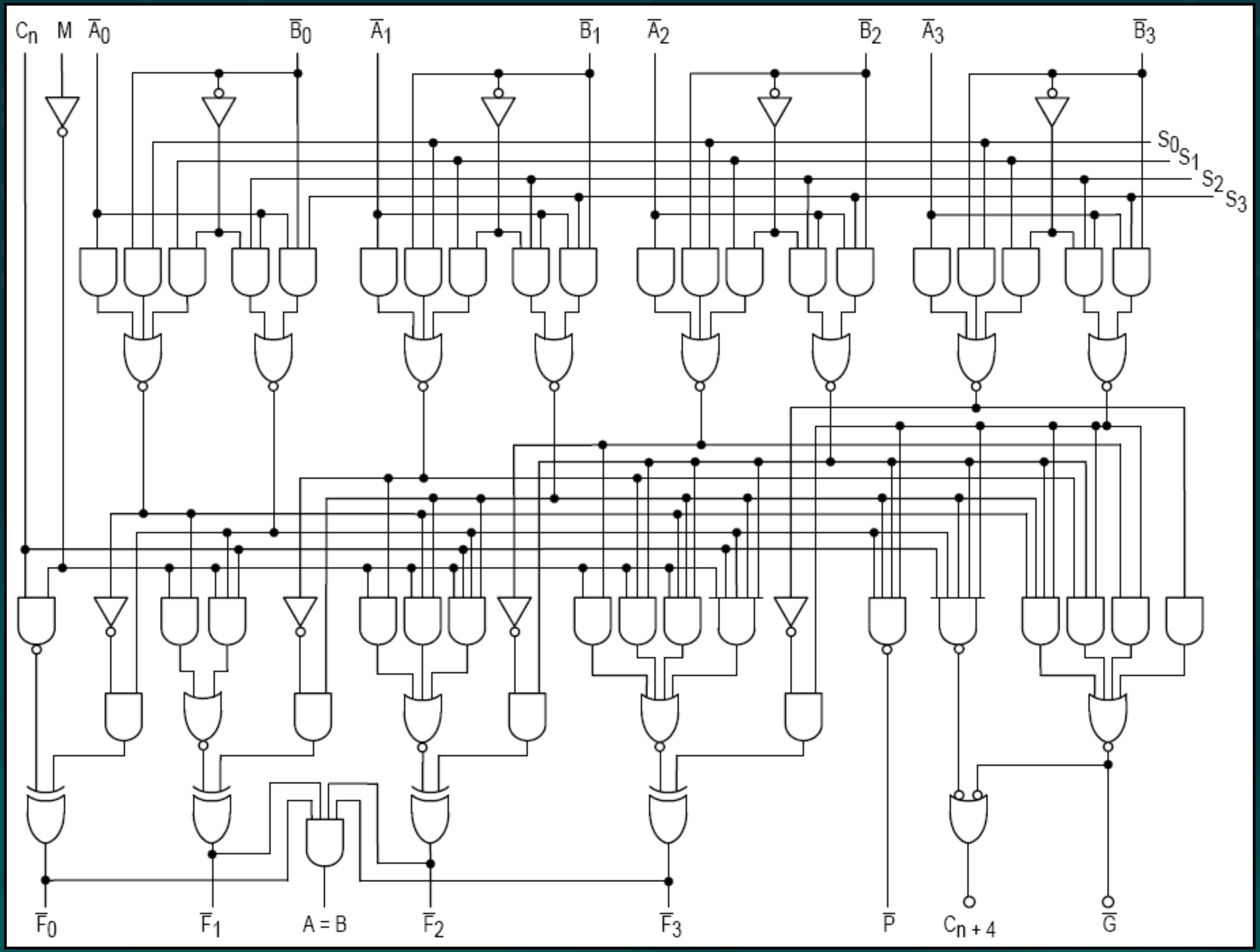






74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!



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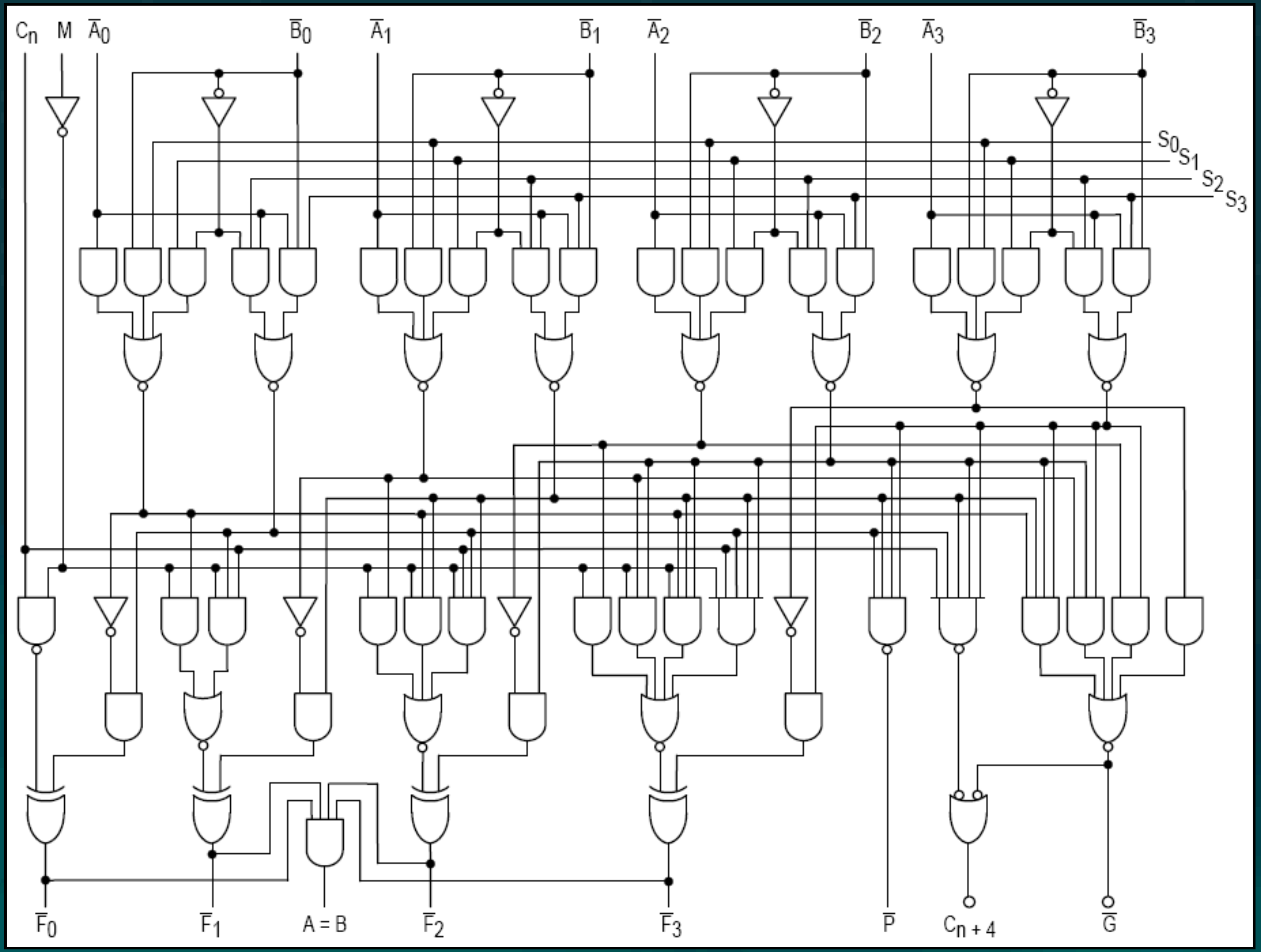
74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!

6+11=17



74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!

6+11=17

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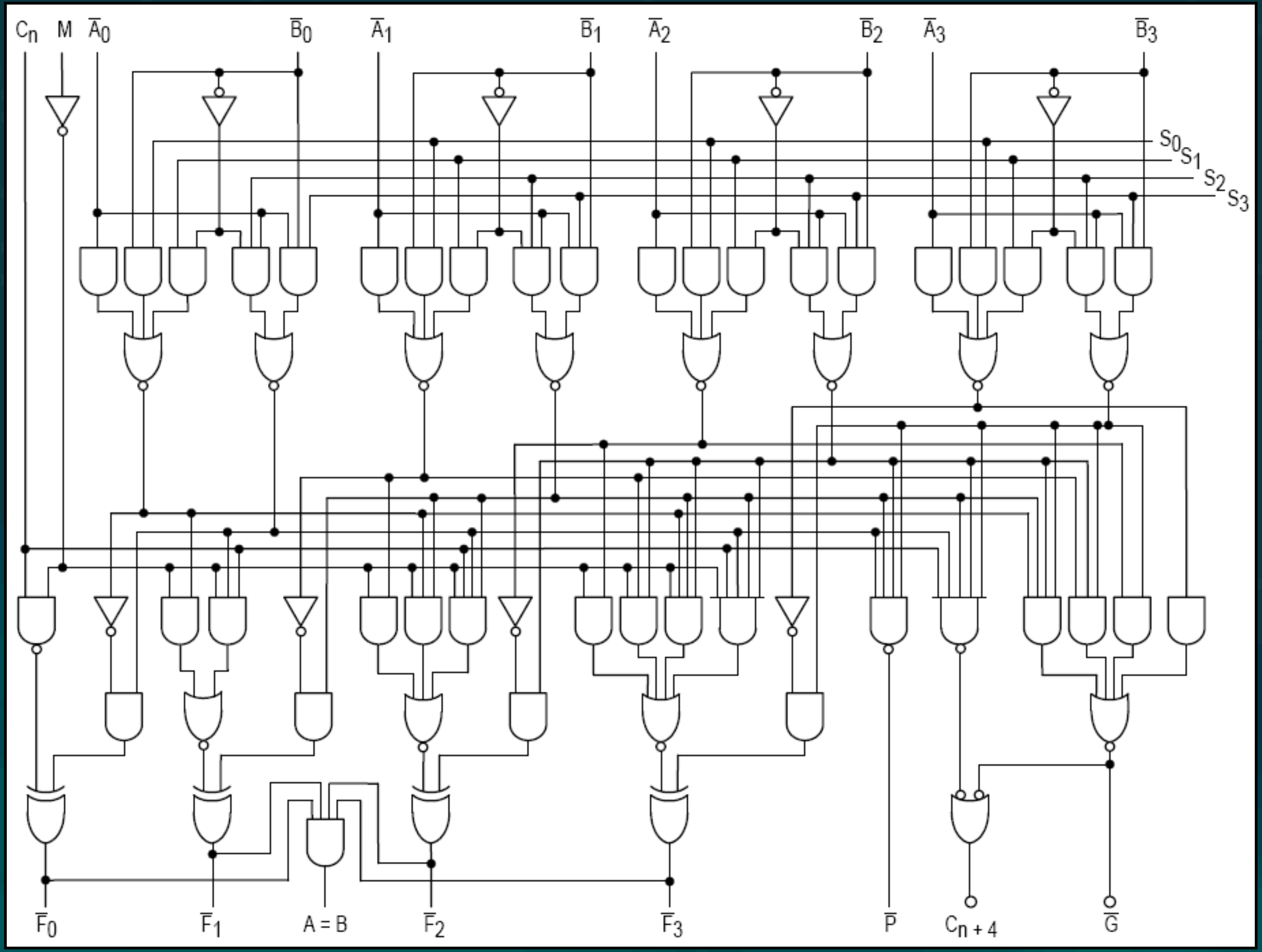

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74181 Arithmetic Logic Unit (ALU) 1969

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6+11=17

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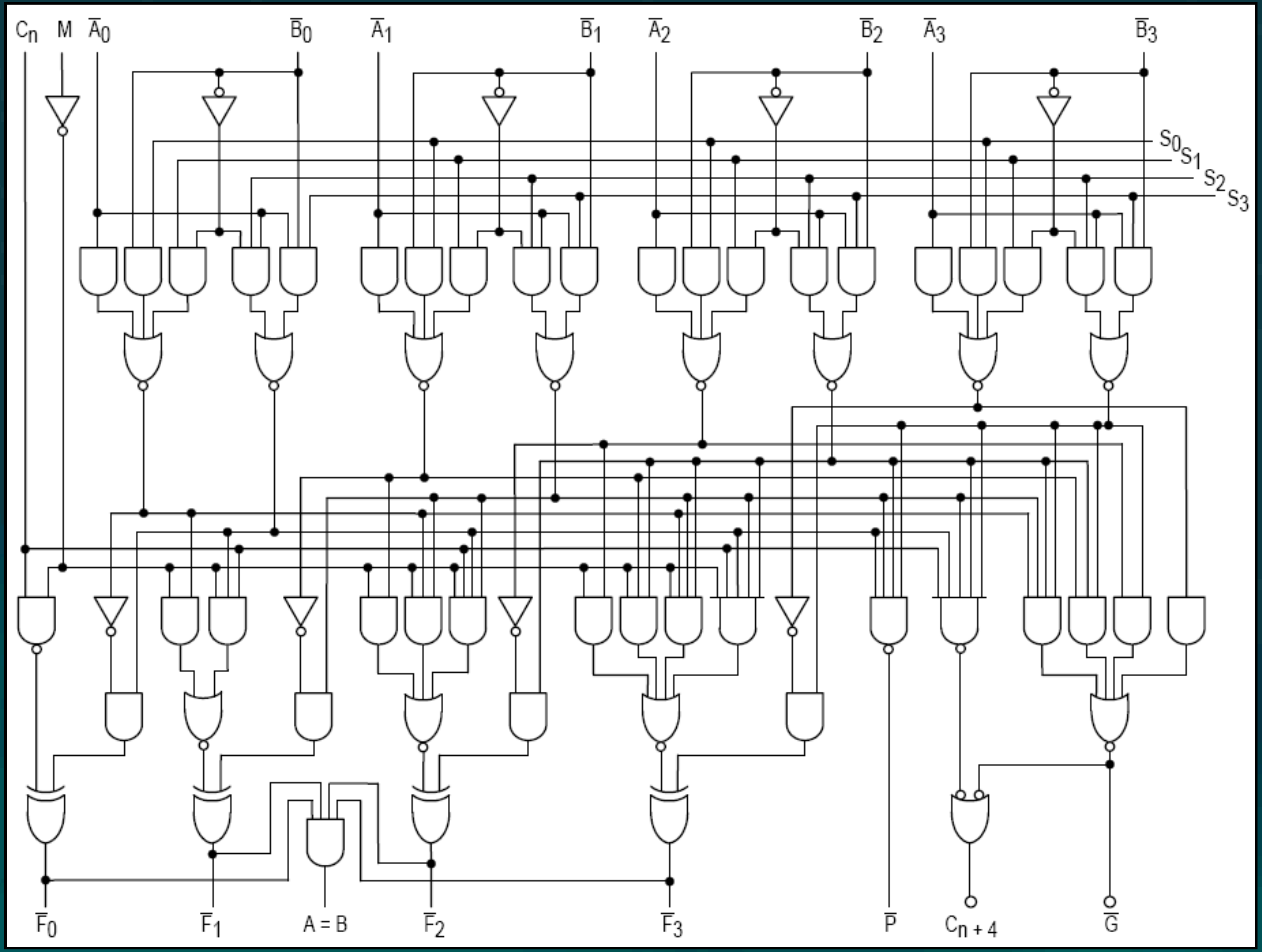

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6+11=17

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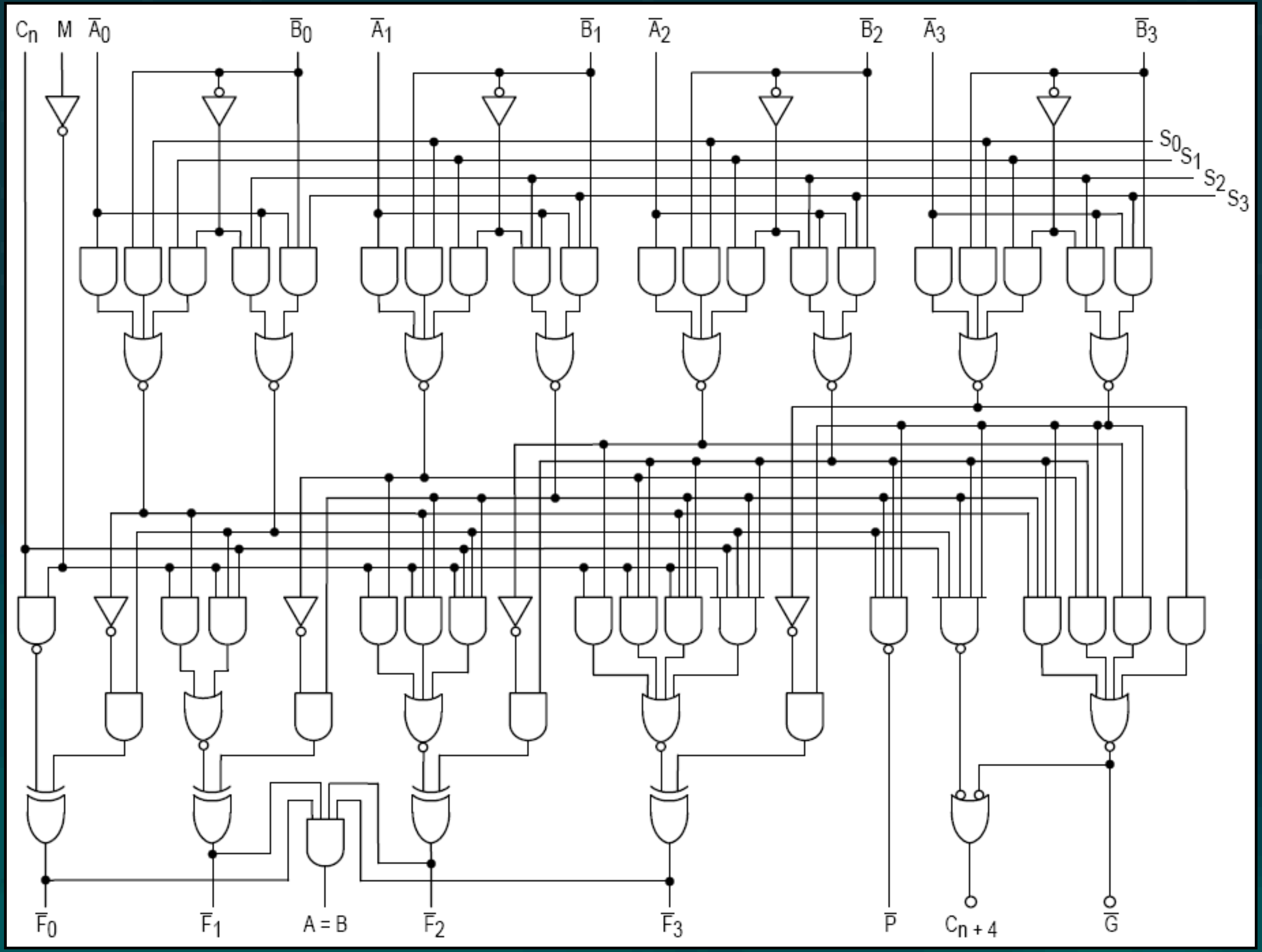

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74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!

6+11=17

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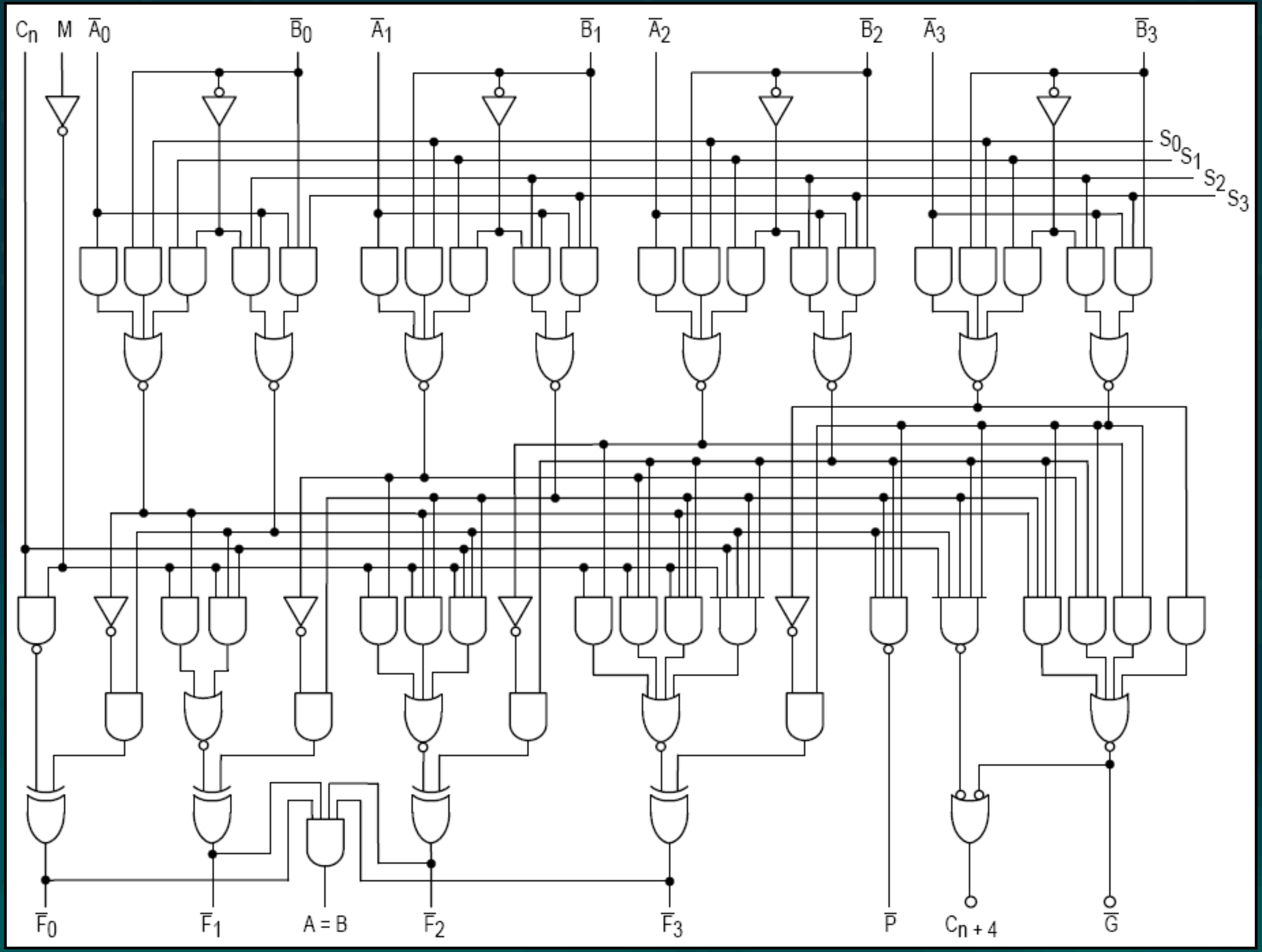

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74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!

6+11=17

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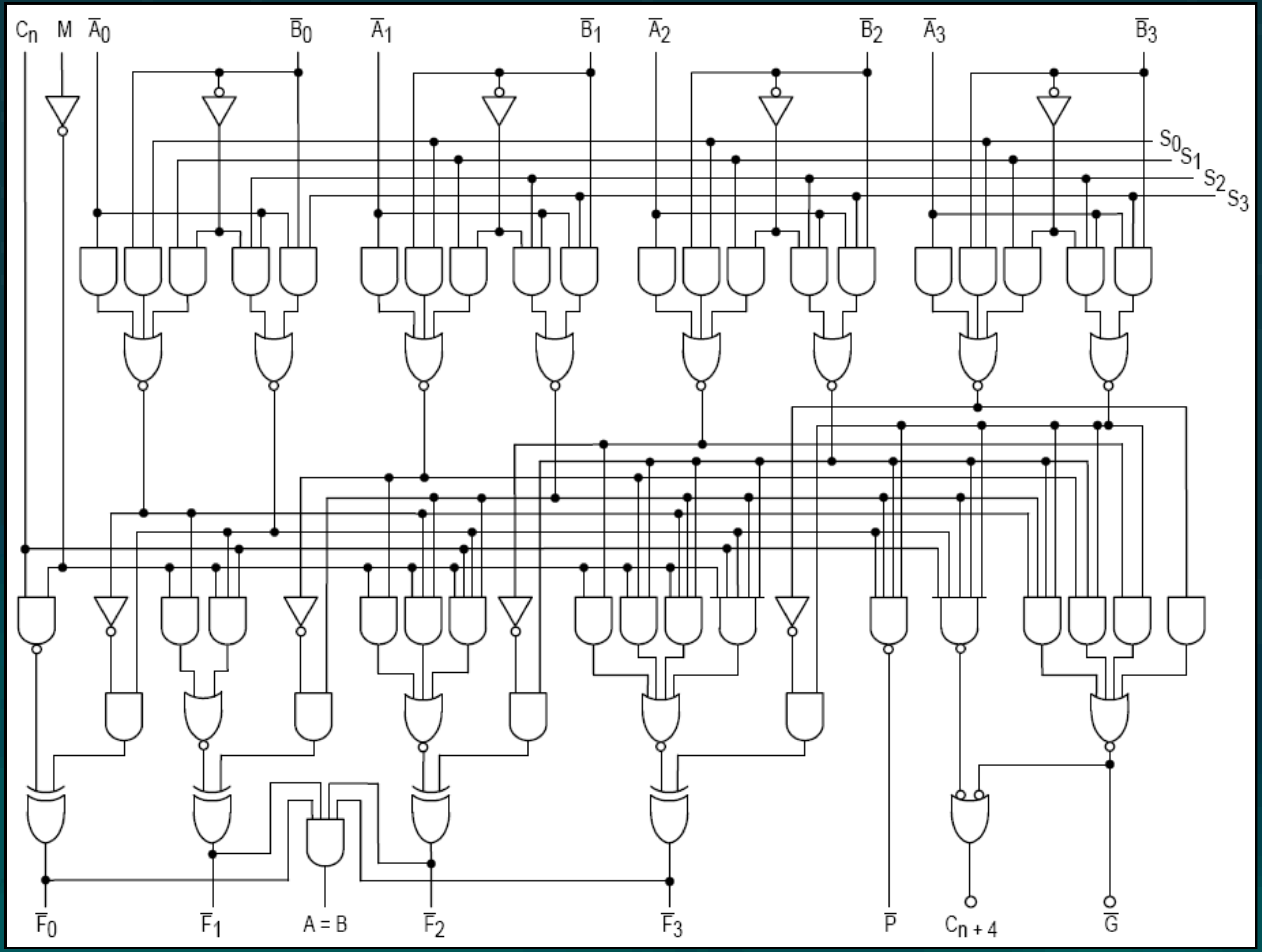

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Only calculates two values at the same time!

6+11=17

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 + 1  0  1  1
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   0  0  0  1
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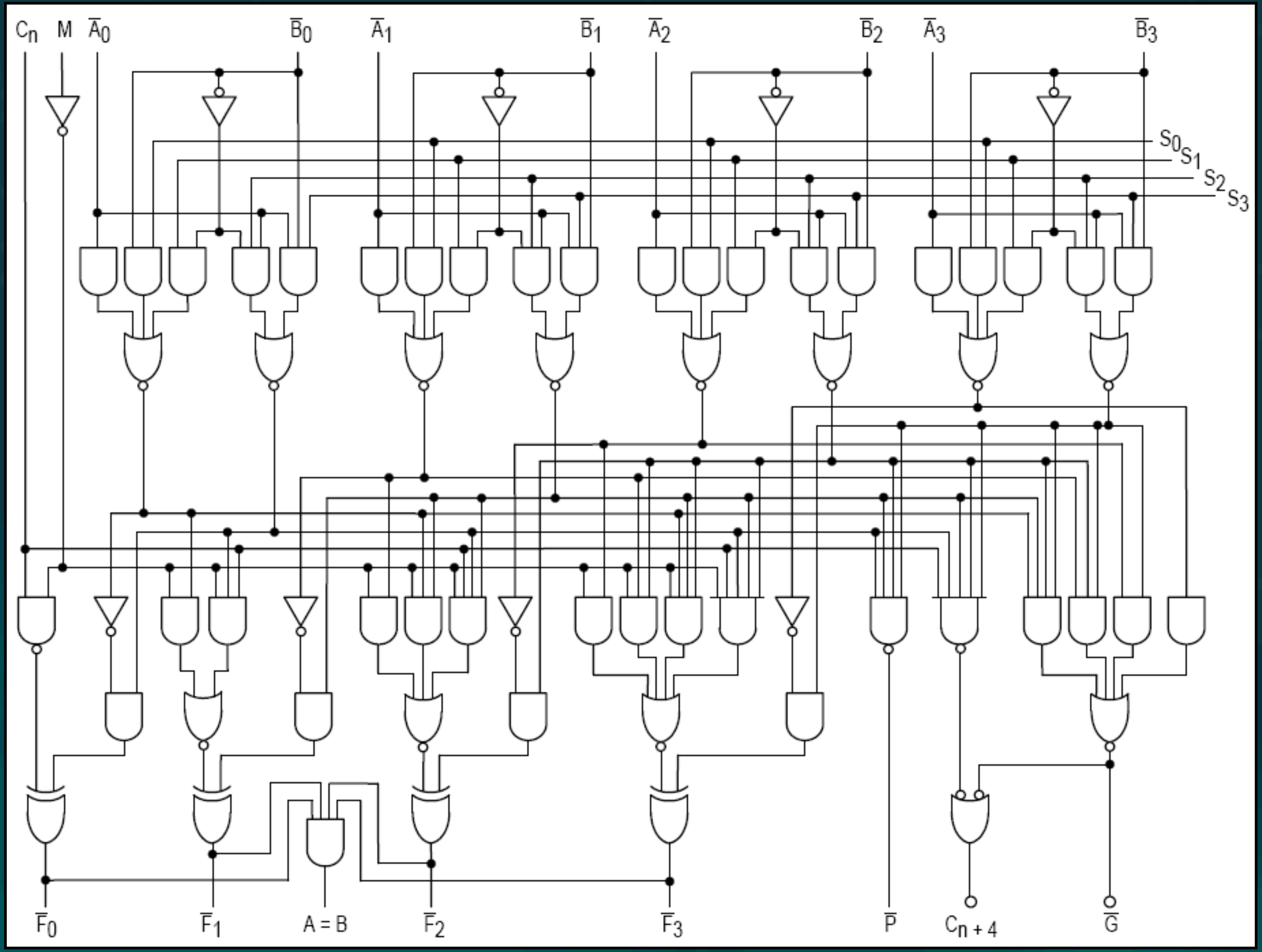
000 1 1 1 1 0 0 1



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1 0 0 0

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6+11=17

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  1  1  1
   0  1  1  0
 + 1  0  1  1
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 1  0  0  0  1
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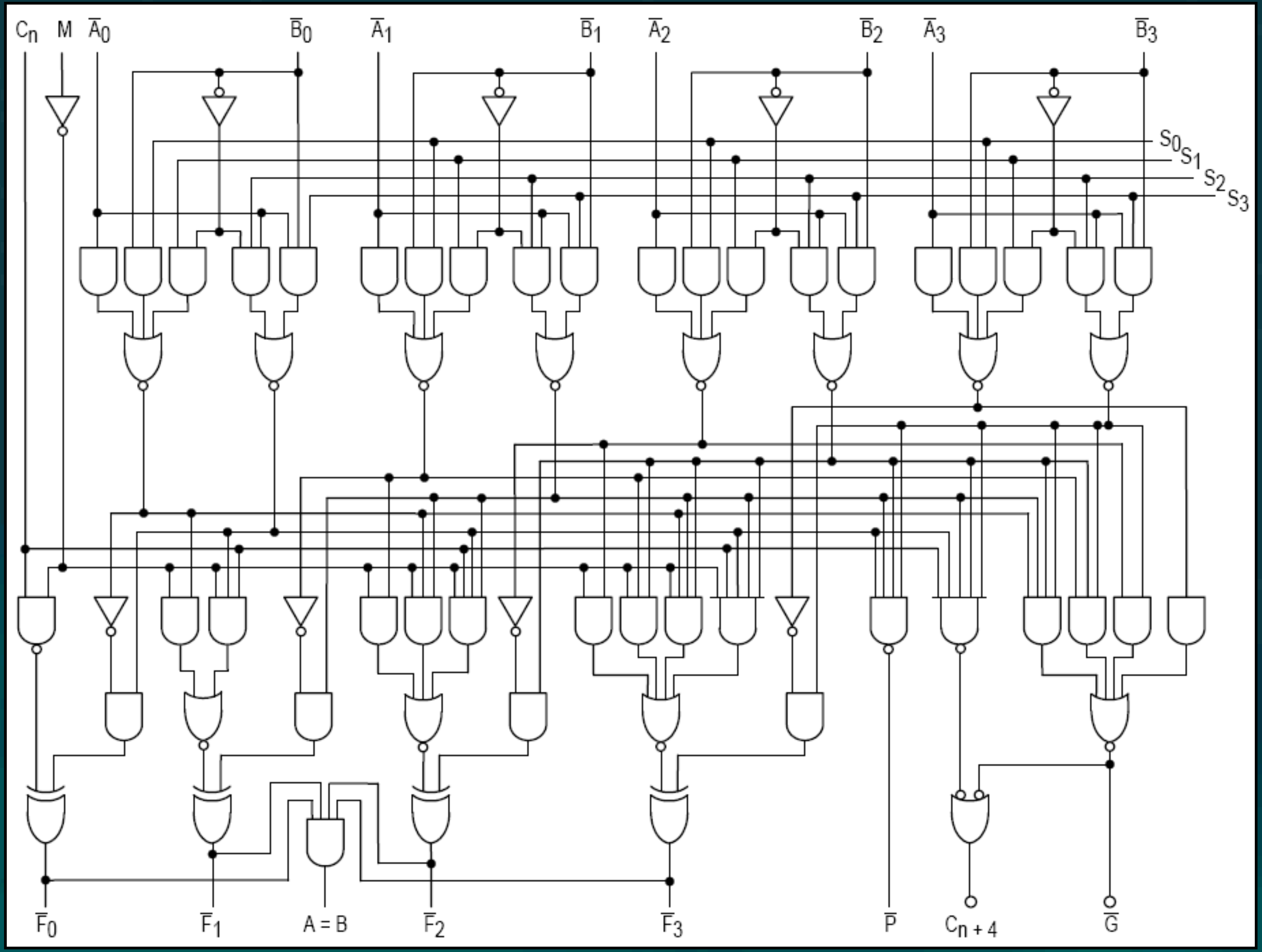
000 1 1 1 1 0 0 1



1001

1 0 0 0 1

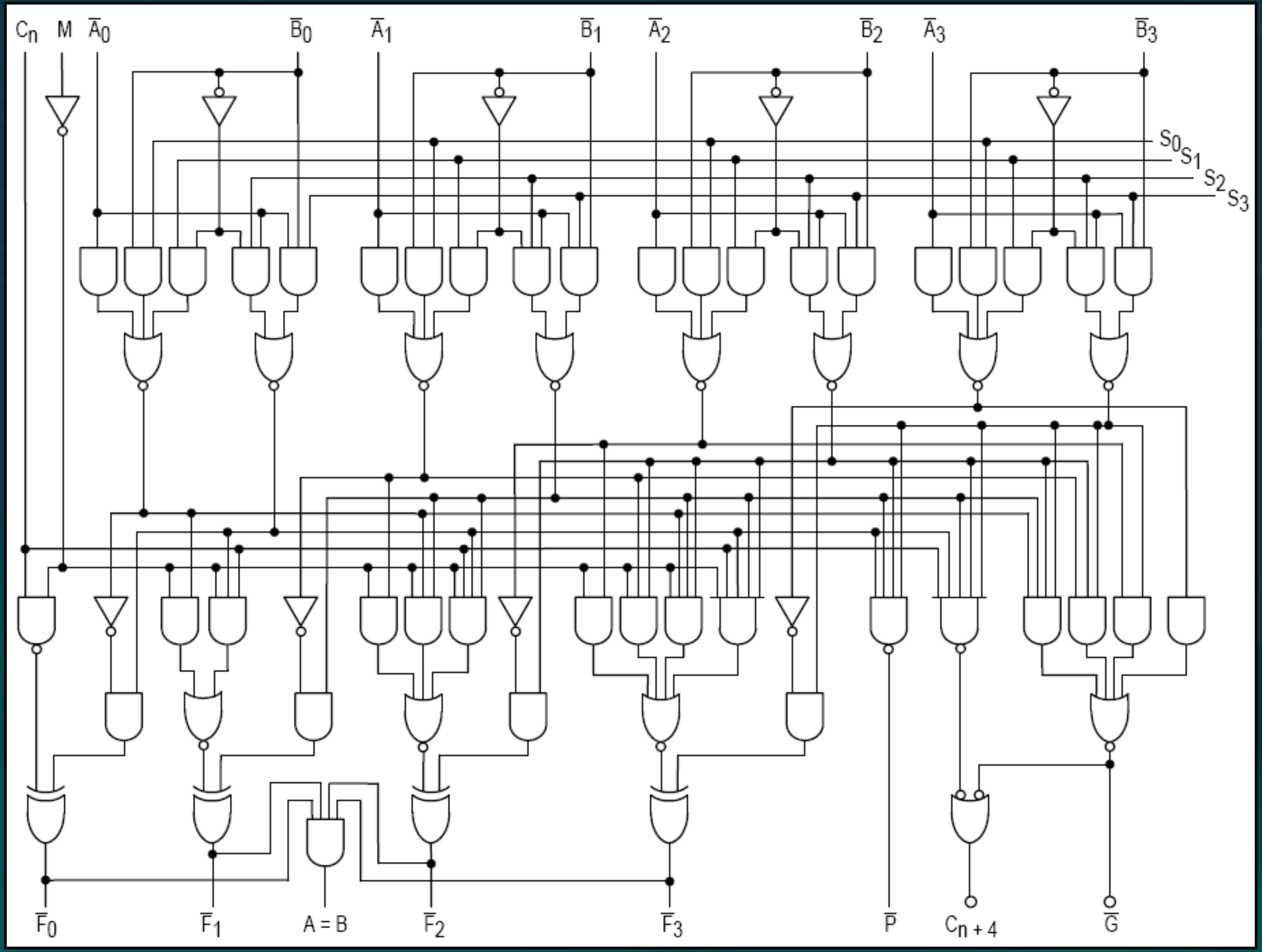
74181 Arithmetic Logic Unit (ALU) 1969

Only calculates two values at the same time!

6+11=17

```
 1  1  1
   0 1 1 0
 + 1 0 1 1
-----------
 1 0 0 0 1
```

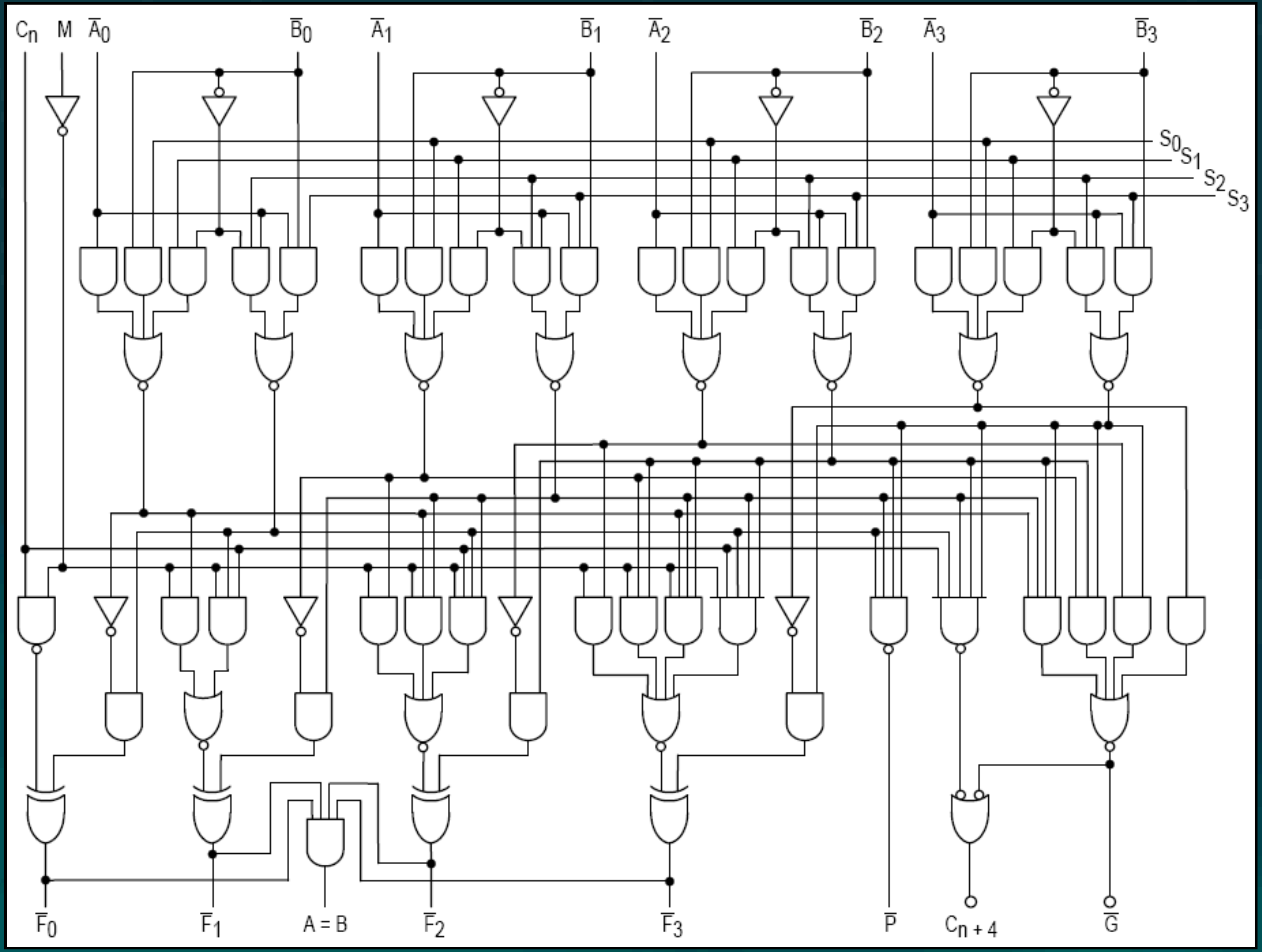
0 0 0 1 1 1 1 0 0 1



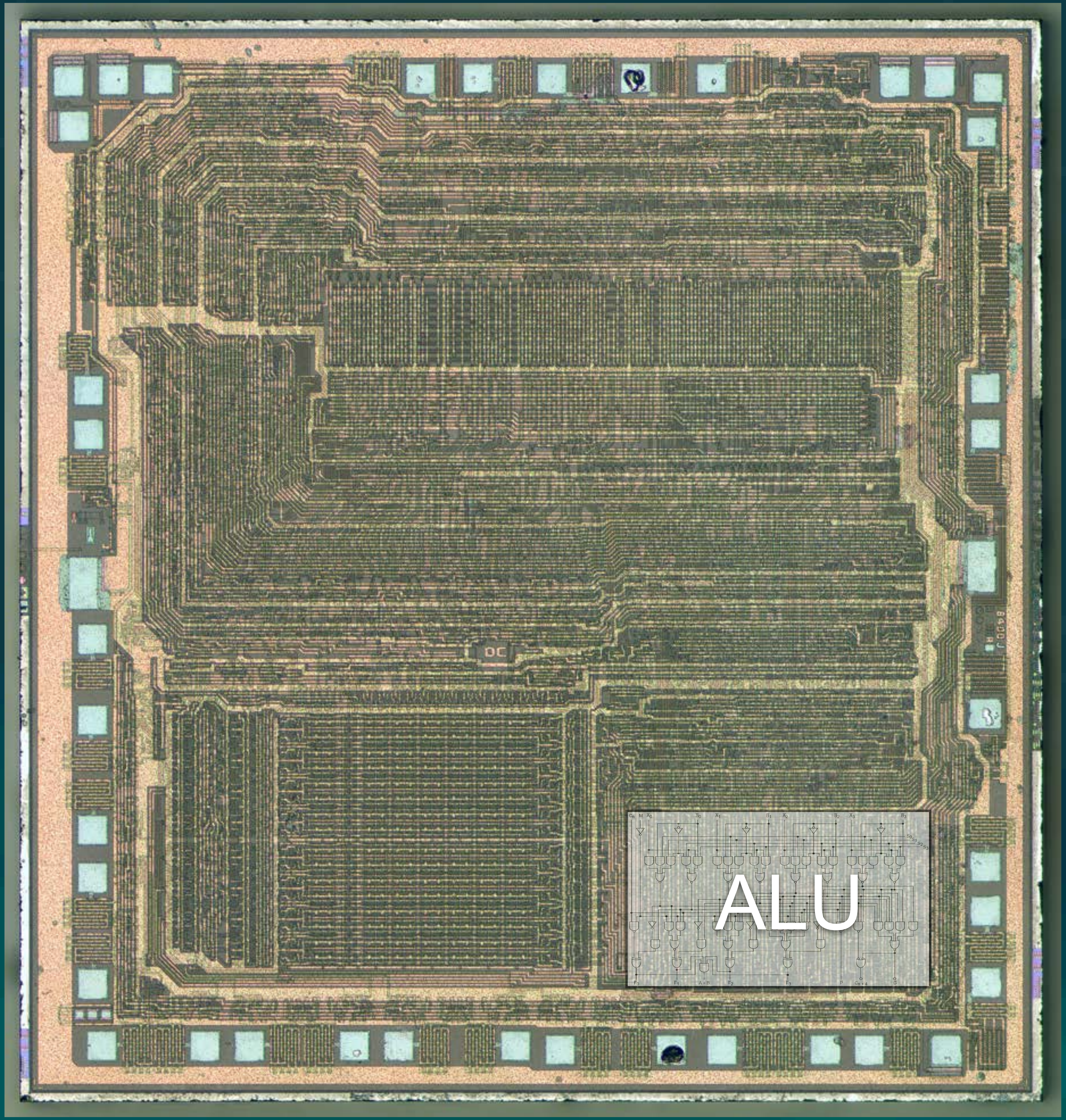
1 0 0 1

1 0 0 0 0 0 1 0

74181 Arithmetic Logic Unit (ALU) 1969



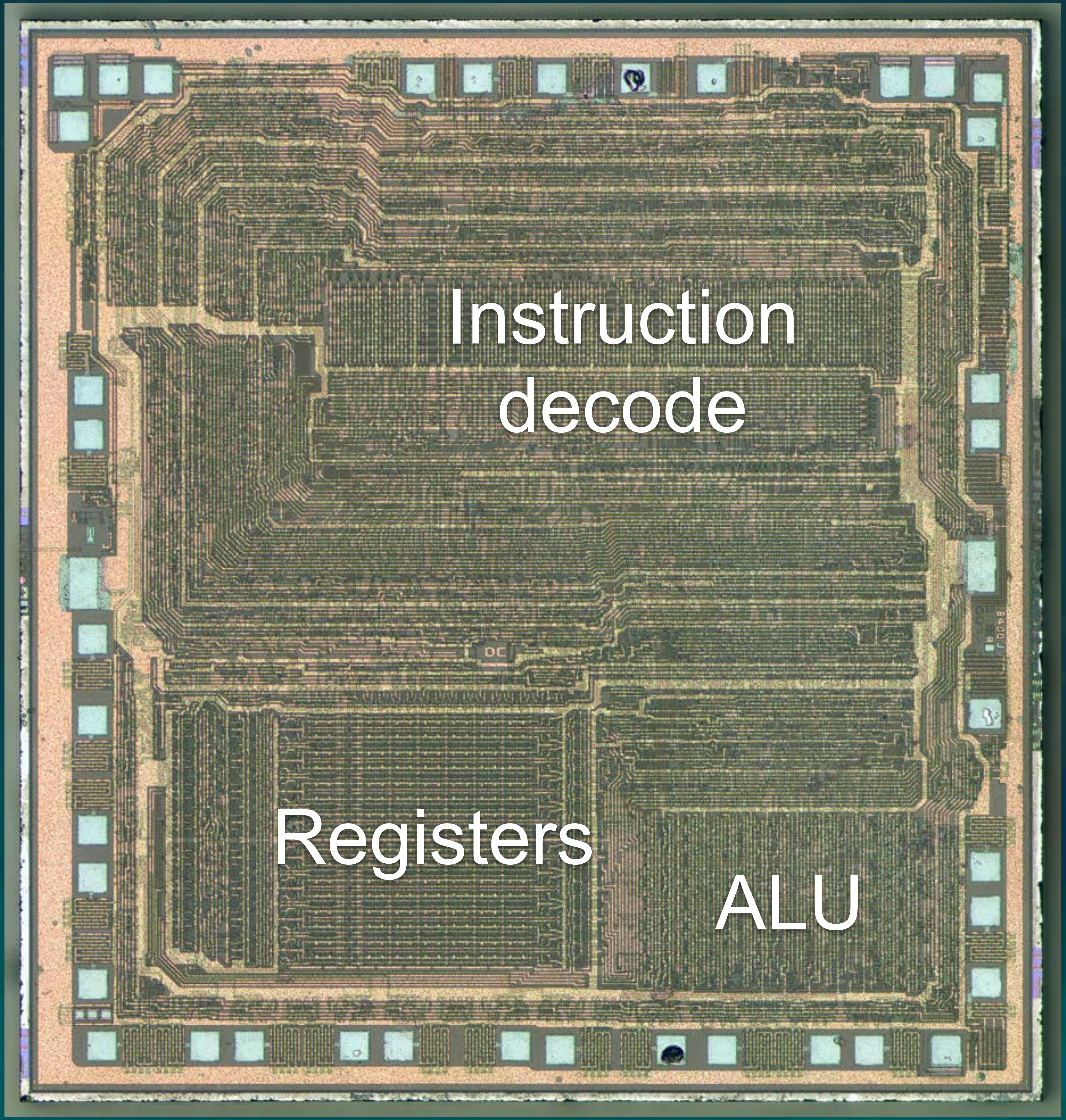
C_n
M
$\overline{A}_0$
$\overline{B}_0$
$\overline{A}_1$
$\overline{B}_1$
$\overline{A}_2$
$\overline{B}_2$
$\overline{A}_3$
$\overline{B}_3$
S_0
S_1
S_2
S_3
$\overline{F}_0$
$\overline{F}_1$
A = B
$\overline{F}_2$
$\overline{F}_3$
$\overline{P}$
C_{n+4}
$\overline{G}$



Z80 processor 1976

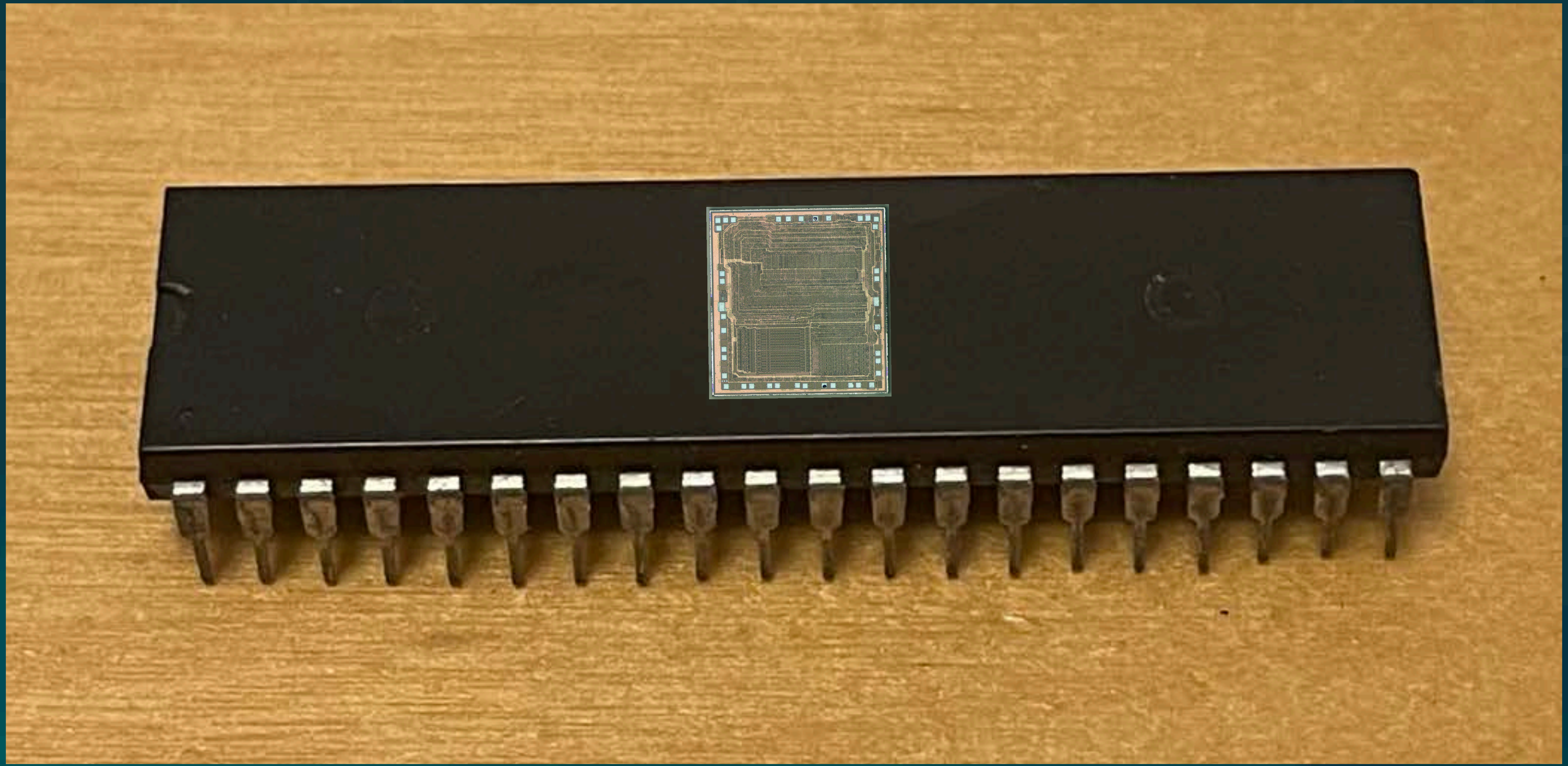
CPU instructions for adding two numbers:

```
LD    A, (x1)
LD    B, A
LD    A, (x2)
ADD   A, B
LD    (x3), A
```

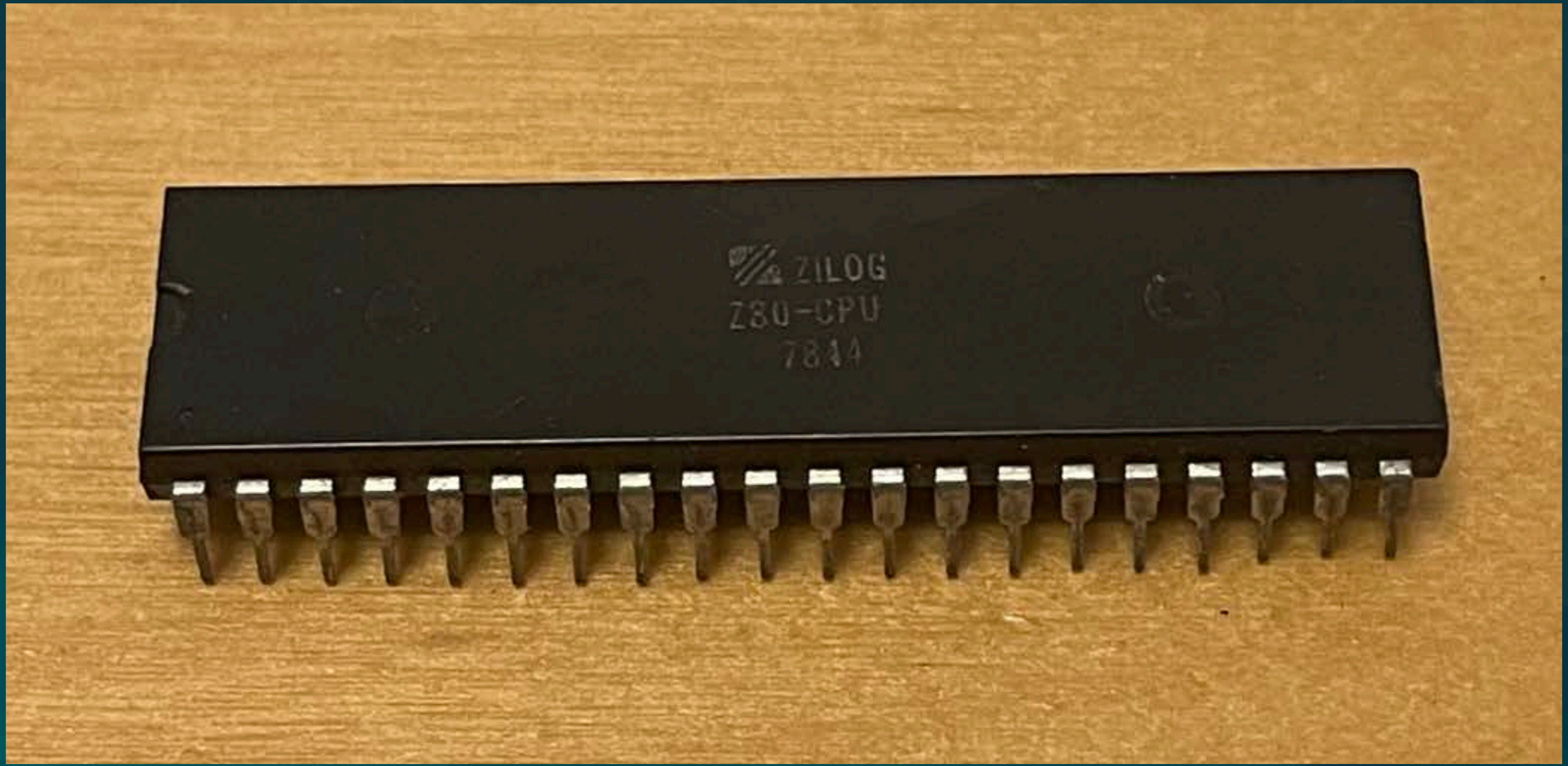


Z80 processor

1976



Z80 processor 1976

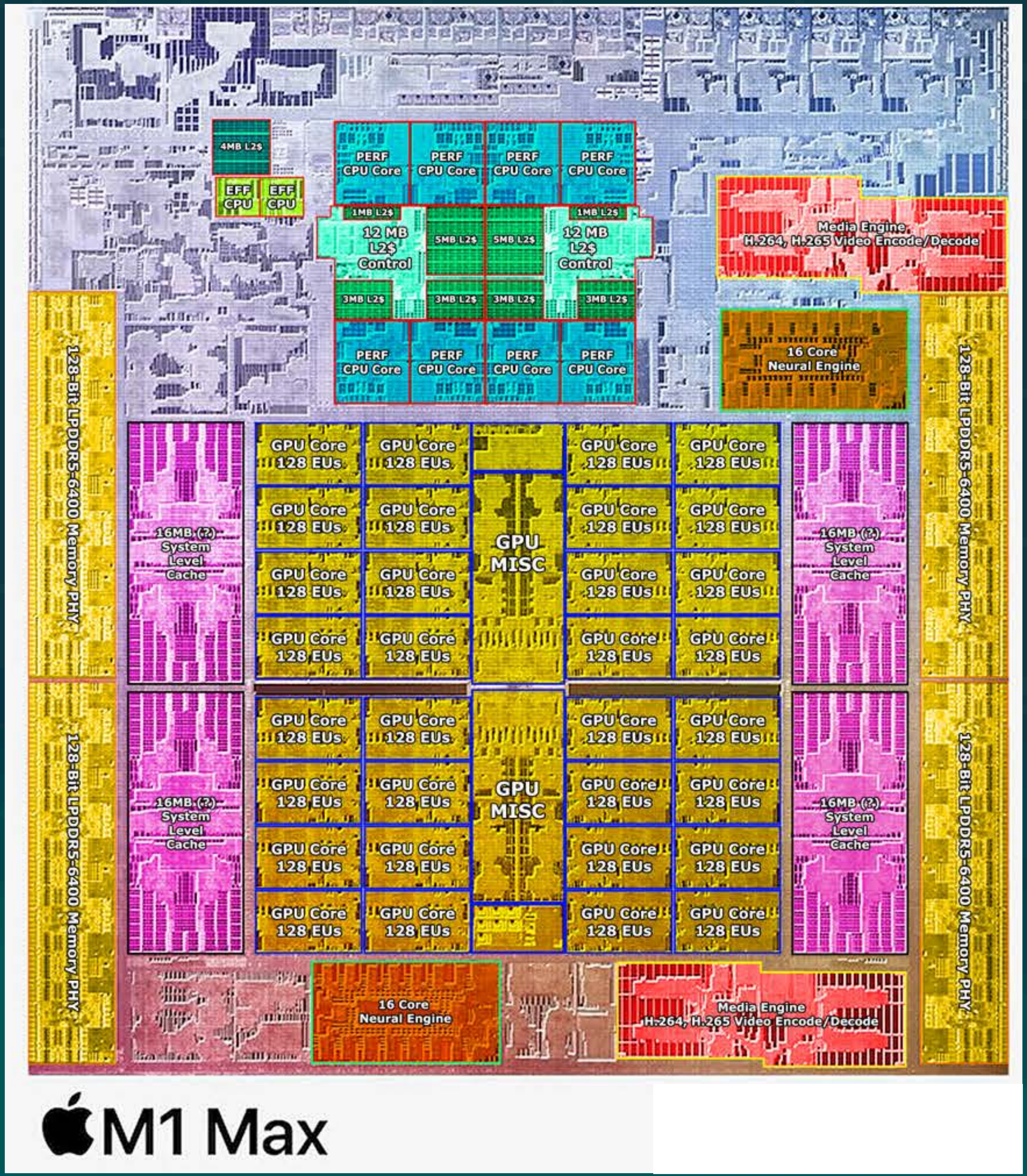


Z80 processor 1976

Modern processor:
Billions of logic gates

But the principle is the same

```
LDRB    w4, [x1]
LDRB    w5, [x2]
ADD     w6, w4, w5
STRB    w6, [x3]
```



How does logistic regression work?

How does logistic regression work?

Console | Background Jobs

R 4.5.1 · ~/Library/CloudStorage/OneDrive-KarolinskaInstitutet/OneDriveR/SAW/

```
> glm(treatment ~ age + sex + relapse + country + relapse*country,data=datadf,family=binomial)
```

Logistic regression

P(treatment=1) ~ age + sex + relapse

age

sex →

previous relapse

$$Treatment = 0 \rightarrow Drug_A$$
$$Treatment = 1 \rightarrow Drug_B$$

Logistic regression

$$x = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix}$$

P(treatment=1) ~ age + sex + relapse

intercept $x_1 = 1$

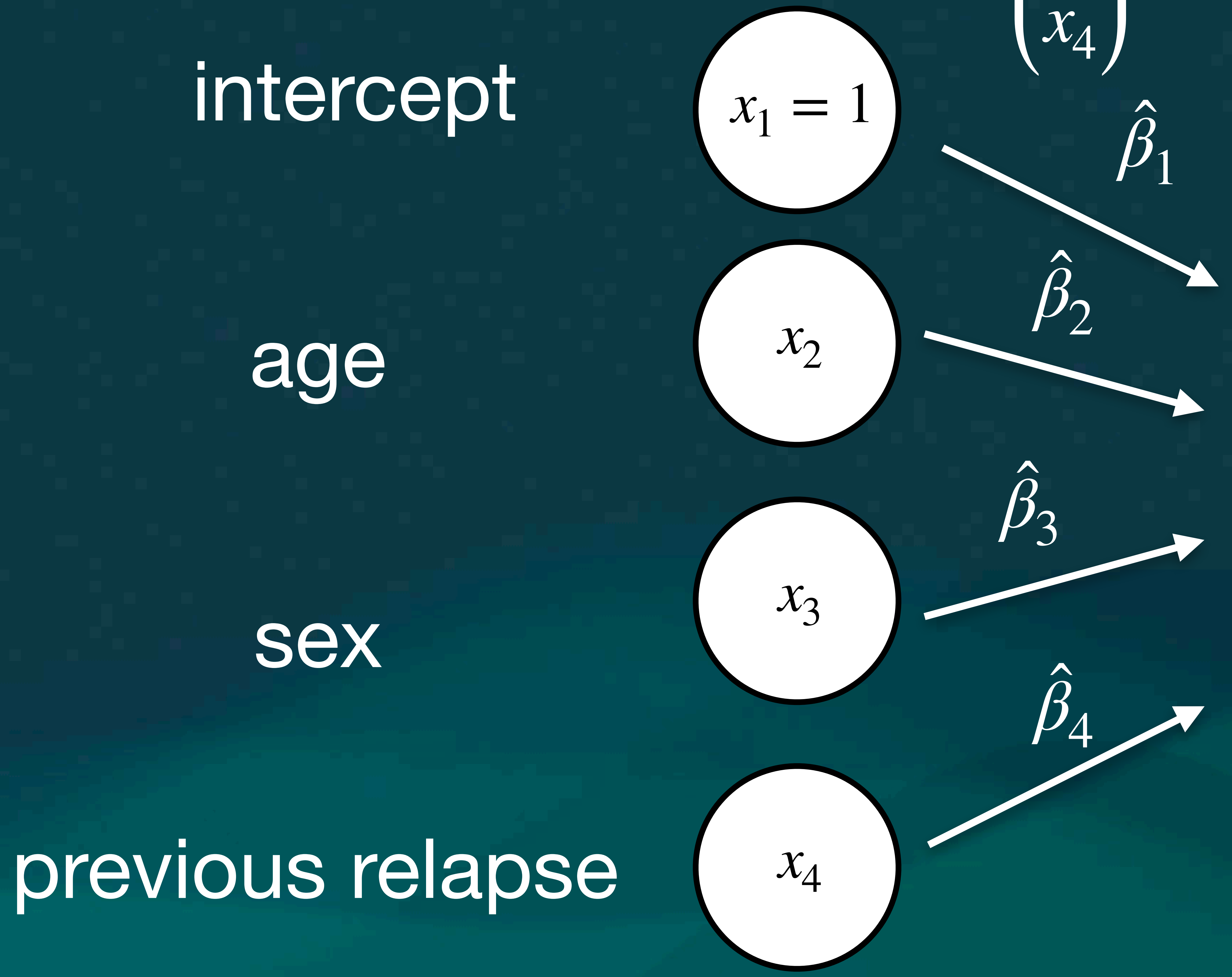
age x_2

sex x_3

previous relapse x_4

Logistic regression

$$x = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} \quad \hat{\beta} = \begin{pmatrix} 1.5 \\ 2.0 \\ 0.3 \\ 1.3 \end{pmatrix}$$



Logistic regression

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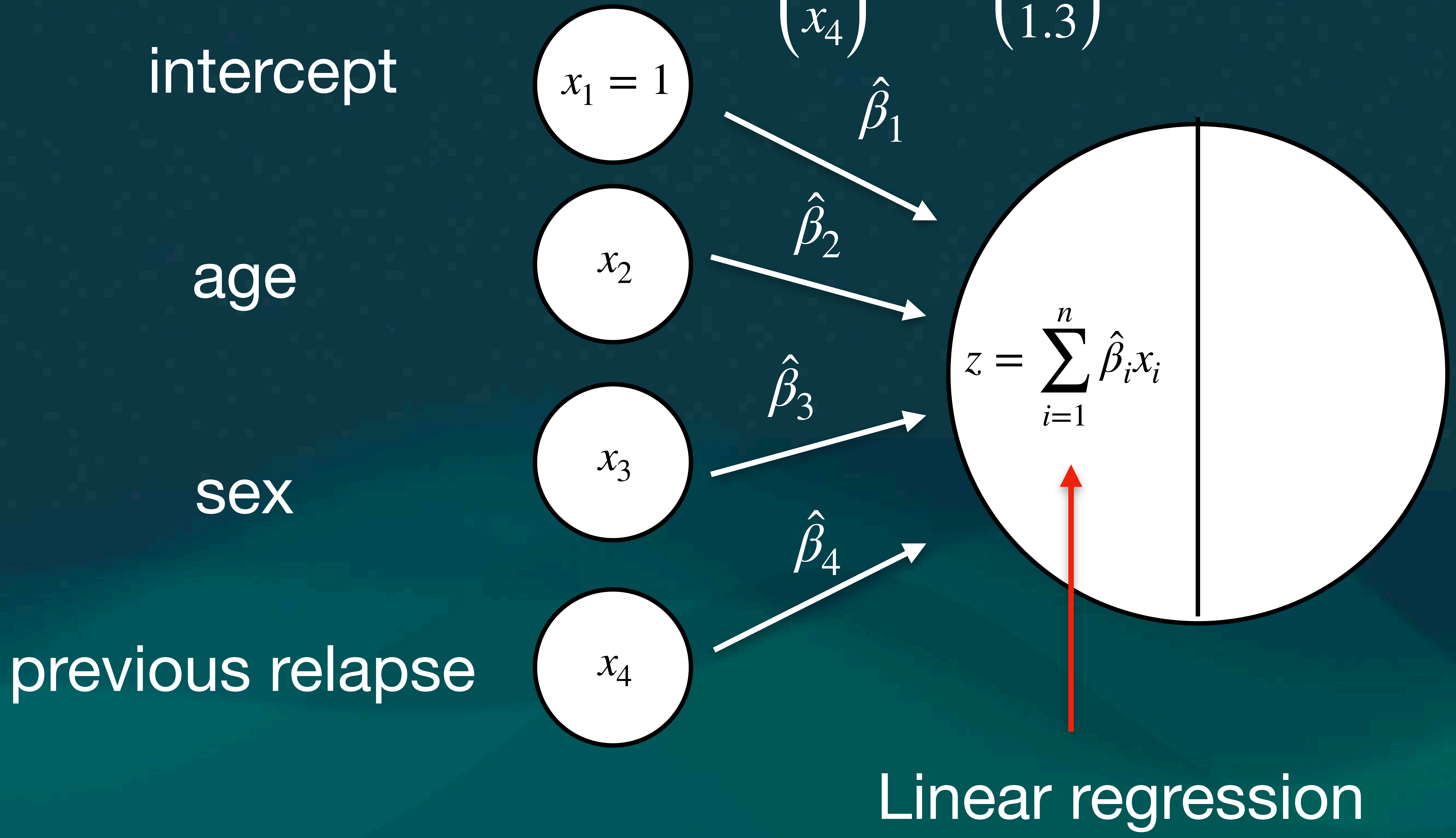

Logistic regression

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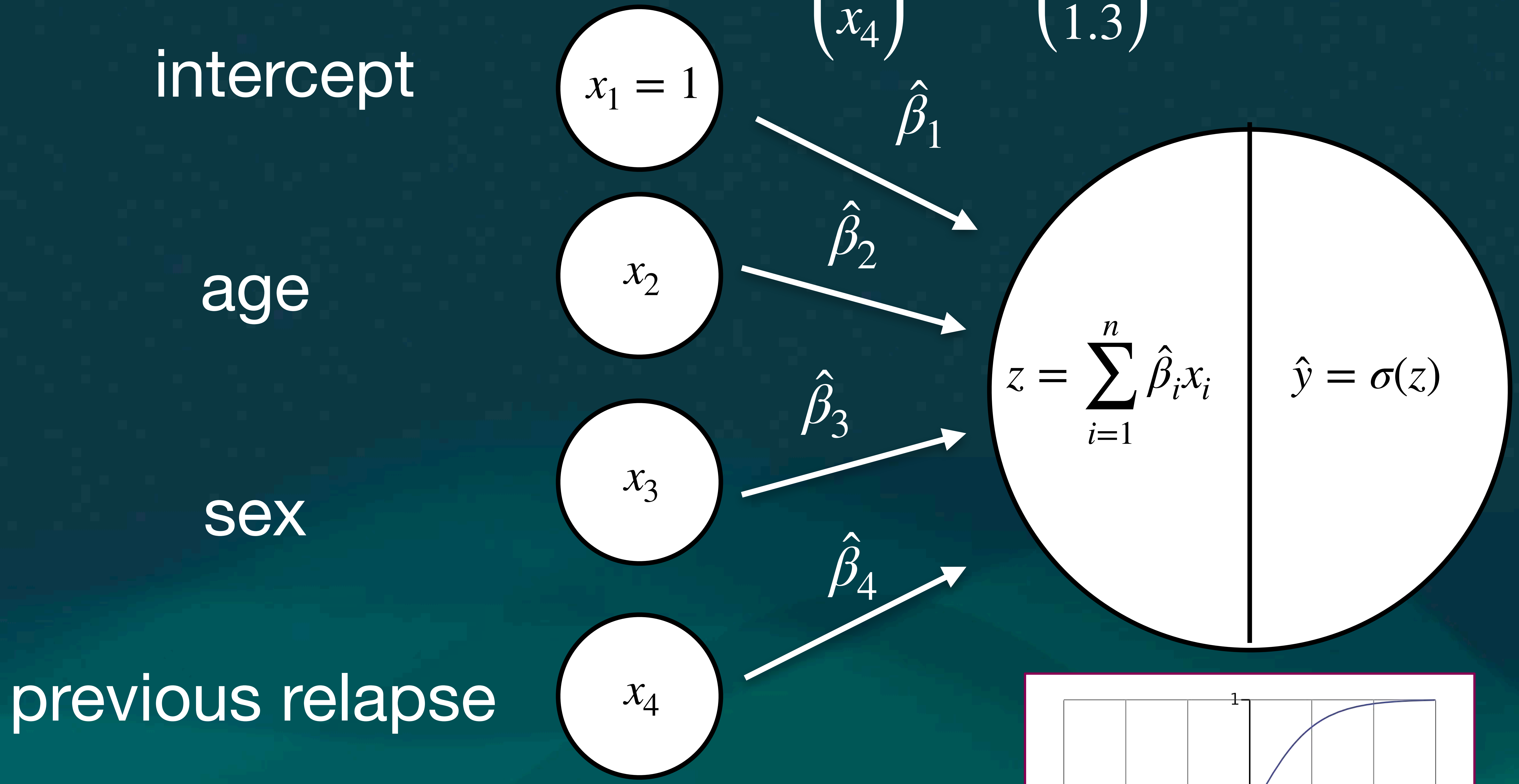
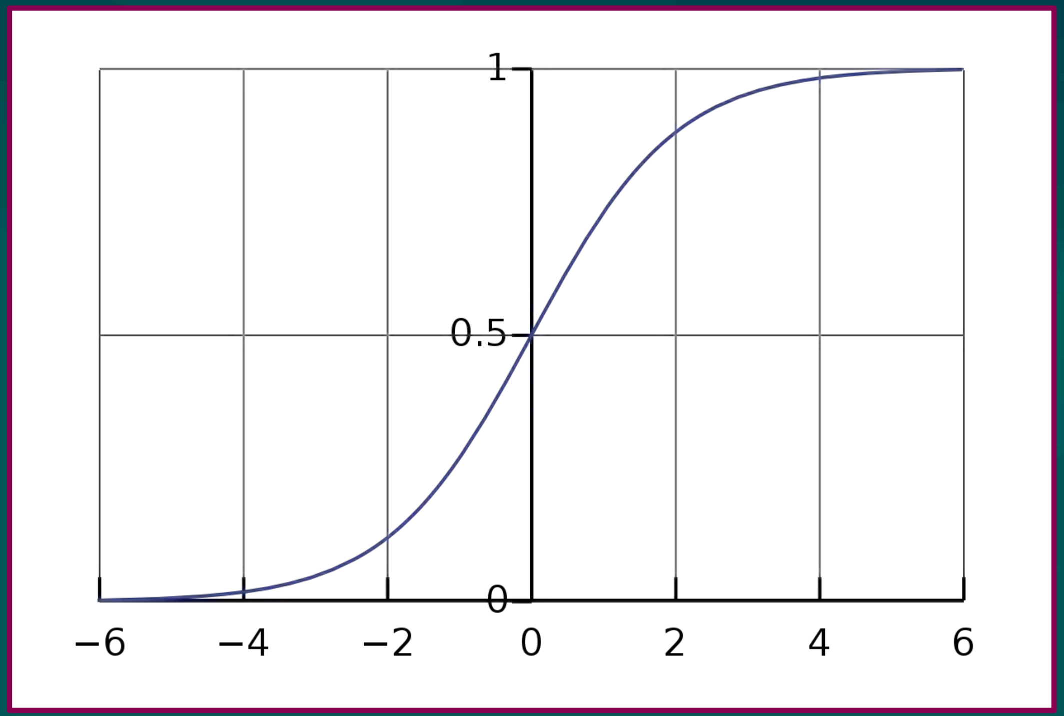


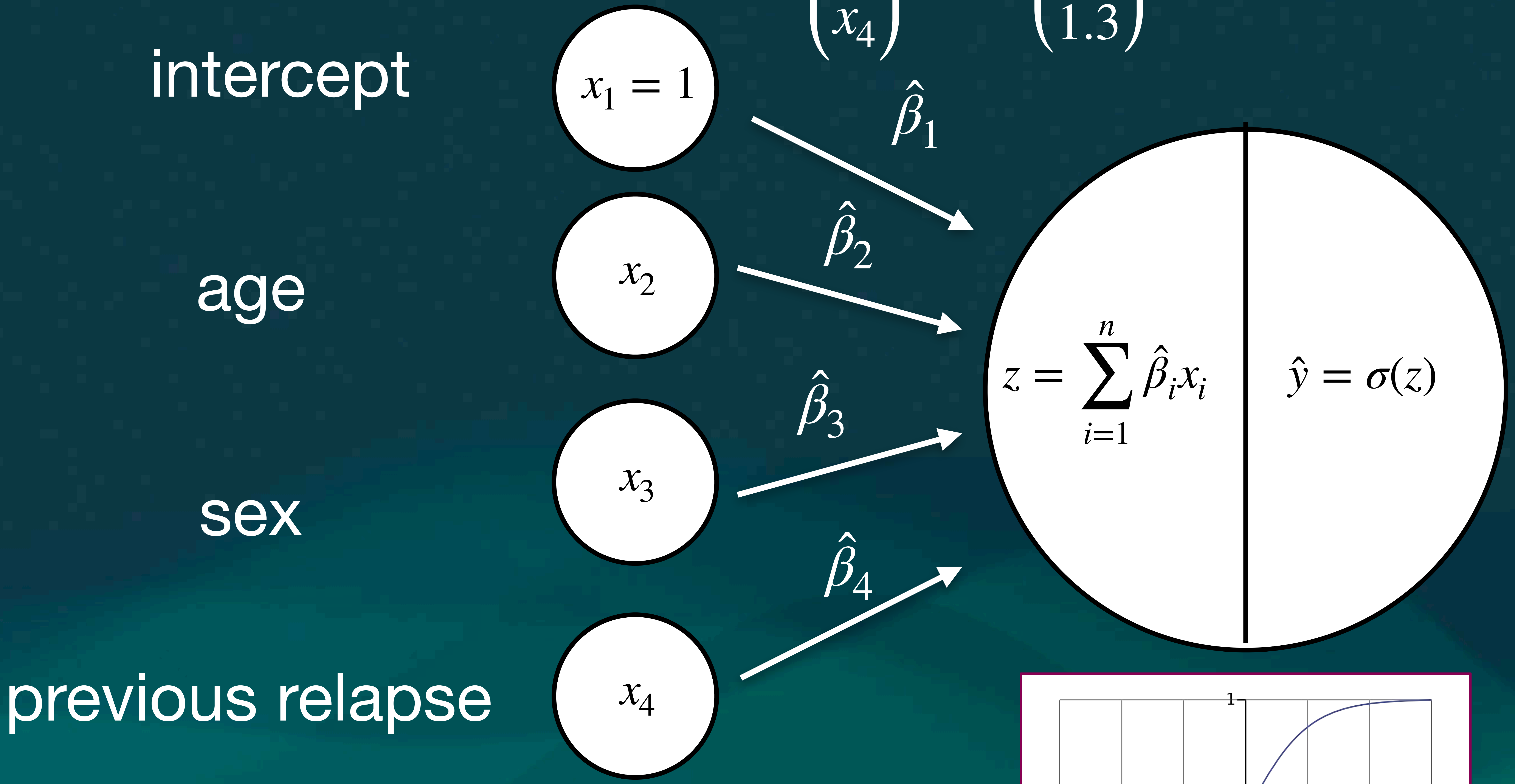


Sigmoid activation function:

$$\sigma(z) = \frac{1}{1 + e^{-z}}$$

Logistic regression

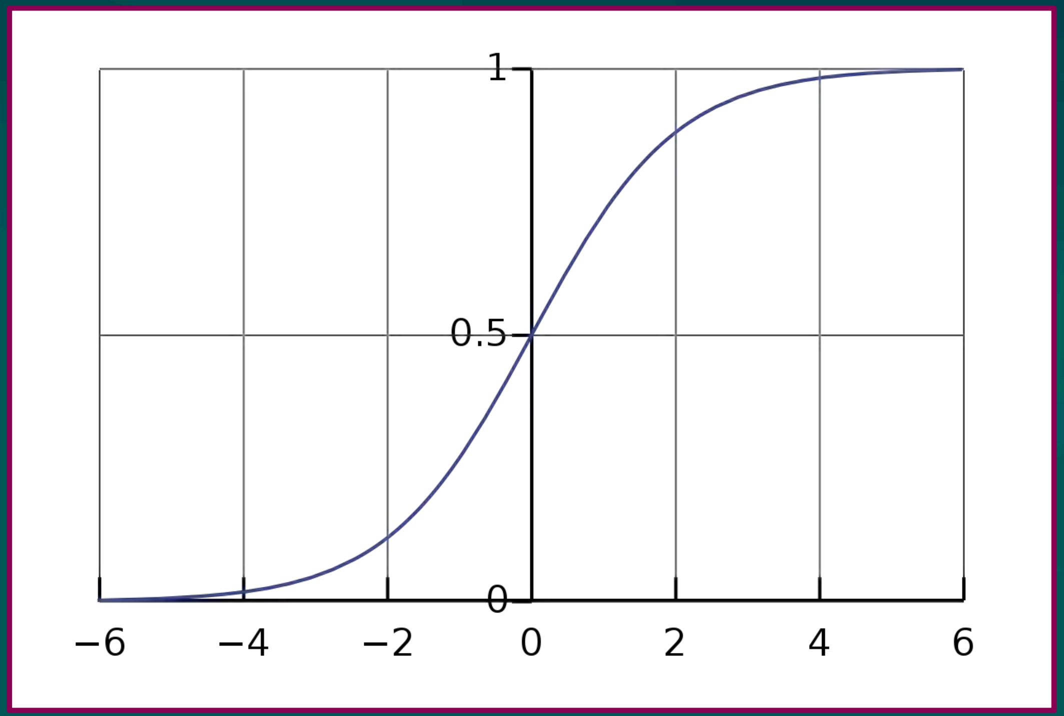
$$x = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} \quad \hat{\beta} = \begin{pmatrix} 1.5 \\ 2.0 \\ 0.3 \\ 1.3 \end{pmatrix}$$



$$\hat{y} = P(Treatment = 1 \mid X)$$

$$Treatment = 0 \rightarrow Drug_A$$

$$Treatment = 1 \rightarrow Drug_B$$

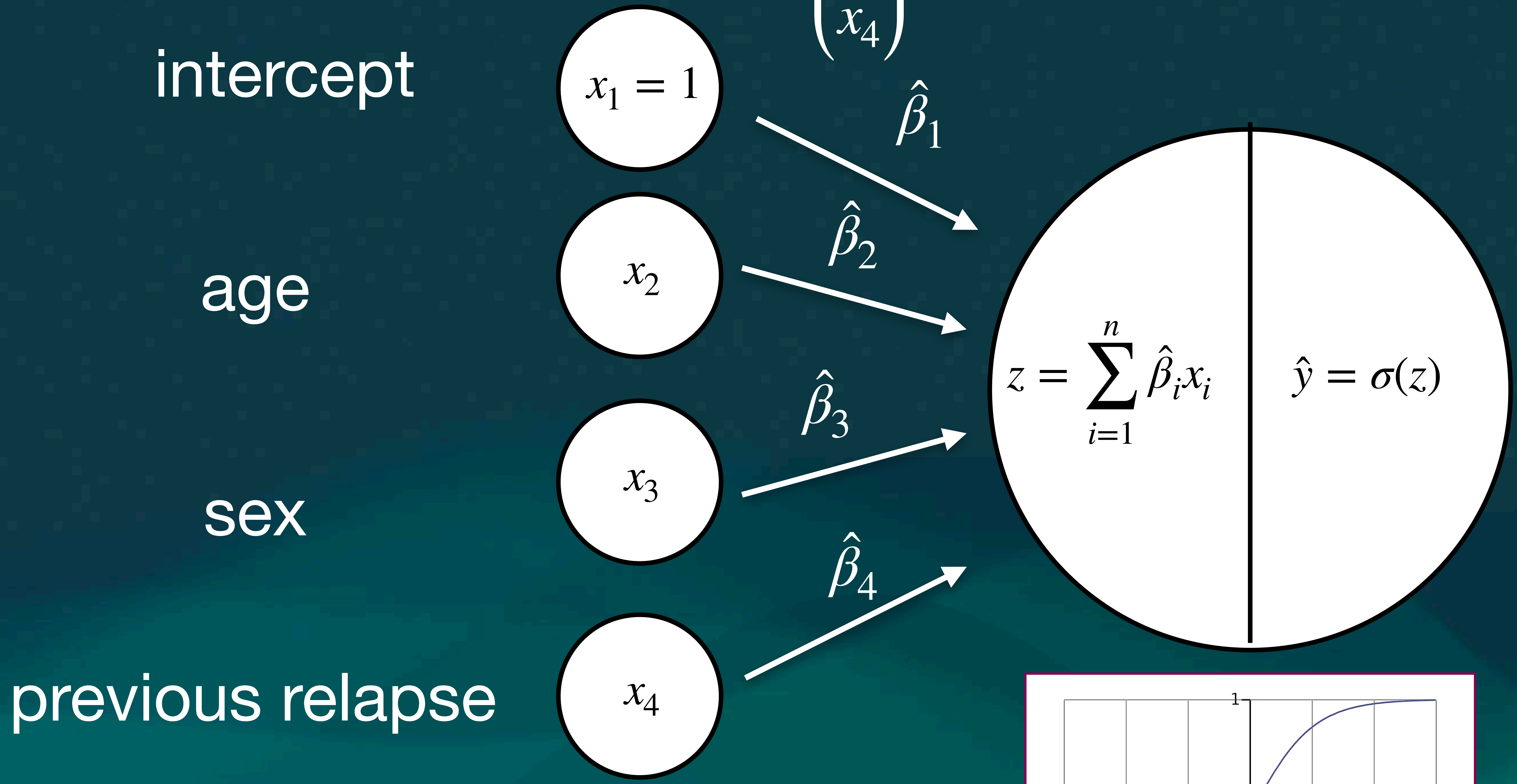


$$\sigma(z) = \frac{1}{1 + e^{-z}}$$

Logistic regression

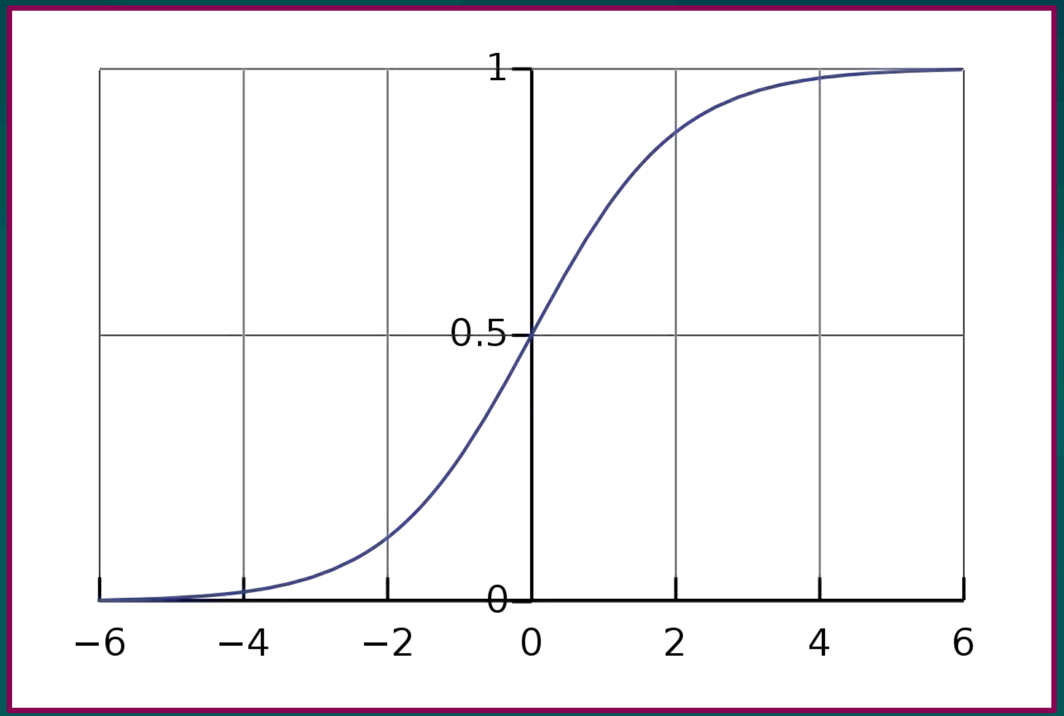
$$x = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix}$$

$$\hat{y} = \frac{1}{1 + e^{-\hat{\beta}^T X}} = \frac{1}{1 + e^{-\hat{\beta}_1 x_1 - \hat{\beta}_2 x_2 - \hat{\beta}_3 x_3 - \hat{\beta}_4 x_4}}$$



$\longrightarrow \hat{y} = P(Treatment = 1 \mid X)$

$$Treatment = 0 \rightarrow Drug_A$$
$$Treatment = 1 \rightarrow Drug_B$$



$$\sigma(z) = \frac{1}{1 + e^{-z}}$$

Logistic regression for patient *i*:

$$\hat{y}_i = \frac{1}{1 + e^{-\hat{\beta}^T X}} = \frac{1}{1 + e^{-\hat{\beta}_1 x_1 - \hat{\beta}_2 x_2 - \hat{\beta}_3 x_3 - \hat{\beta}_4 x_4}}$$

$y_i =$ true treatment

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Across patients, what are the optimal $\hat{\beta}$?

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$y_i =$ true treatment

Across patients, what are the optimal $\hat{\beta}$?

Cost function for patient *i*: $\mathcal{J}_i(\hat{y}_i, y_i) = -\left(y_i \log(\hat{y}_i) + (1 - y_i) \log(1 - \hat{y}_i)\right)$

"the error"

Logistic regression for patient *i:*

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Cost function for all patients: $\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$

We want to reduce the cost

How do we reduce the cost?

$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

How do we reduce the cost?

$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

$$\beta^T = [0\,0\,0\,0]$$

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$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

$$\beta^T = [0\,0\,0\,0]$$

↓

$y_1 = 1,\ \hat{y}_1 = 0.2 \rightarrow \mathcal{J}_1 = 1.6$ High cost value

True Estimated

True value = patient had treatment B

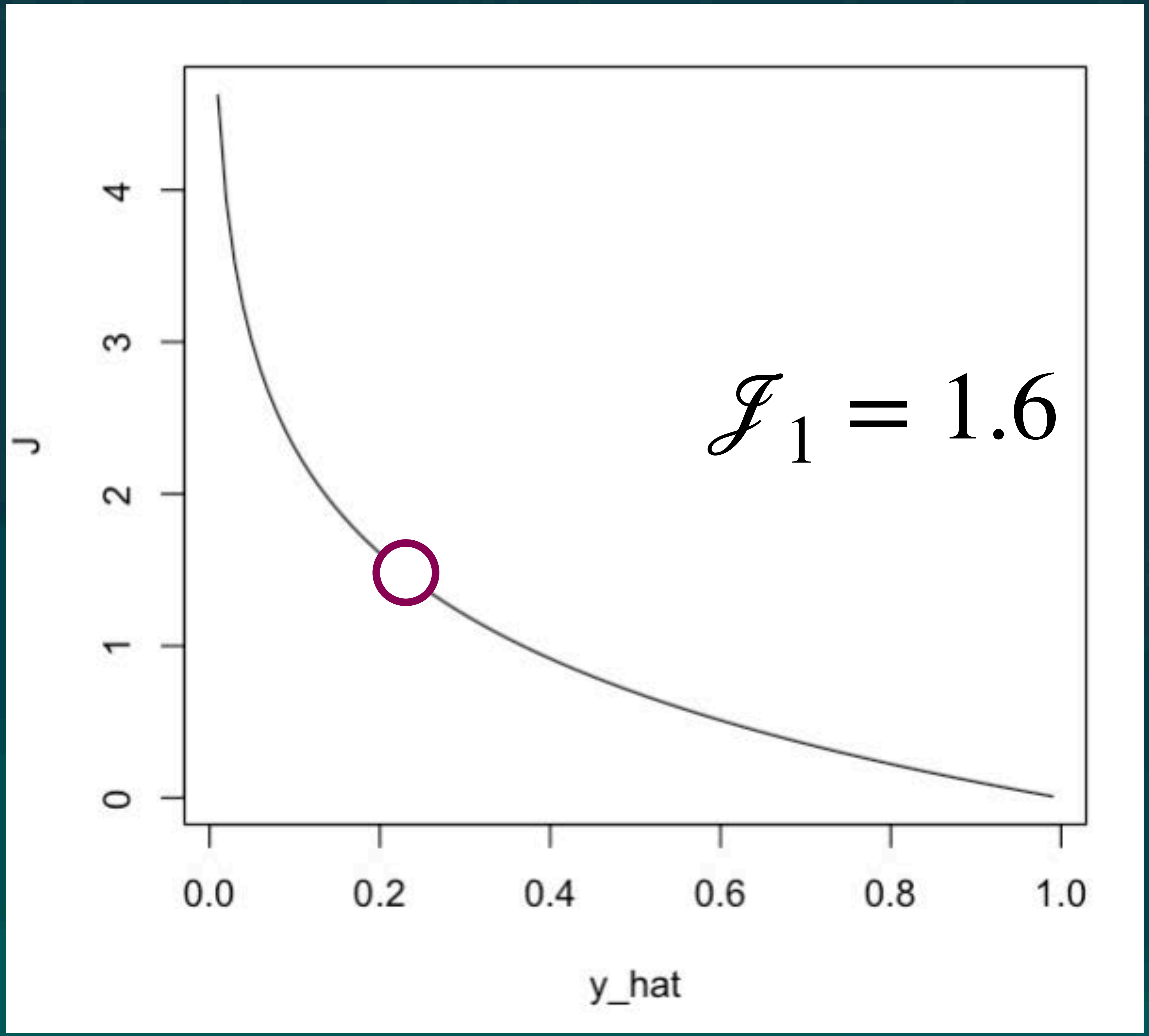
Estimated value = patient had treatment A

How do we reduce the cost?

$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

$$\beta^T = [0\,0\,0\,0]$$

$$y_1 = 1,\ \hat{y}_1 = 0.2 \rightarrow \mathcal{J}_1 = 1.6$$



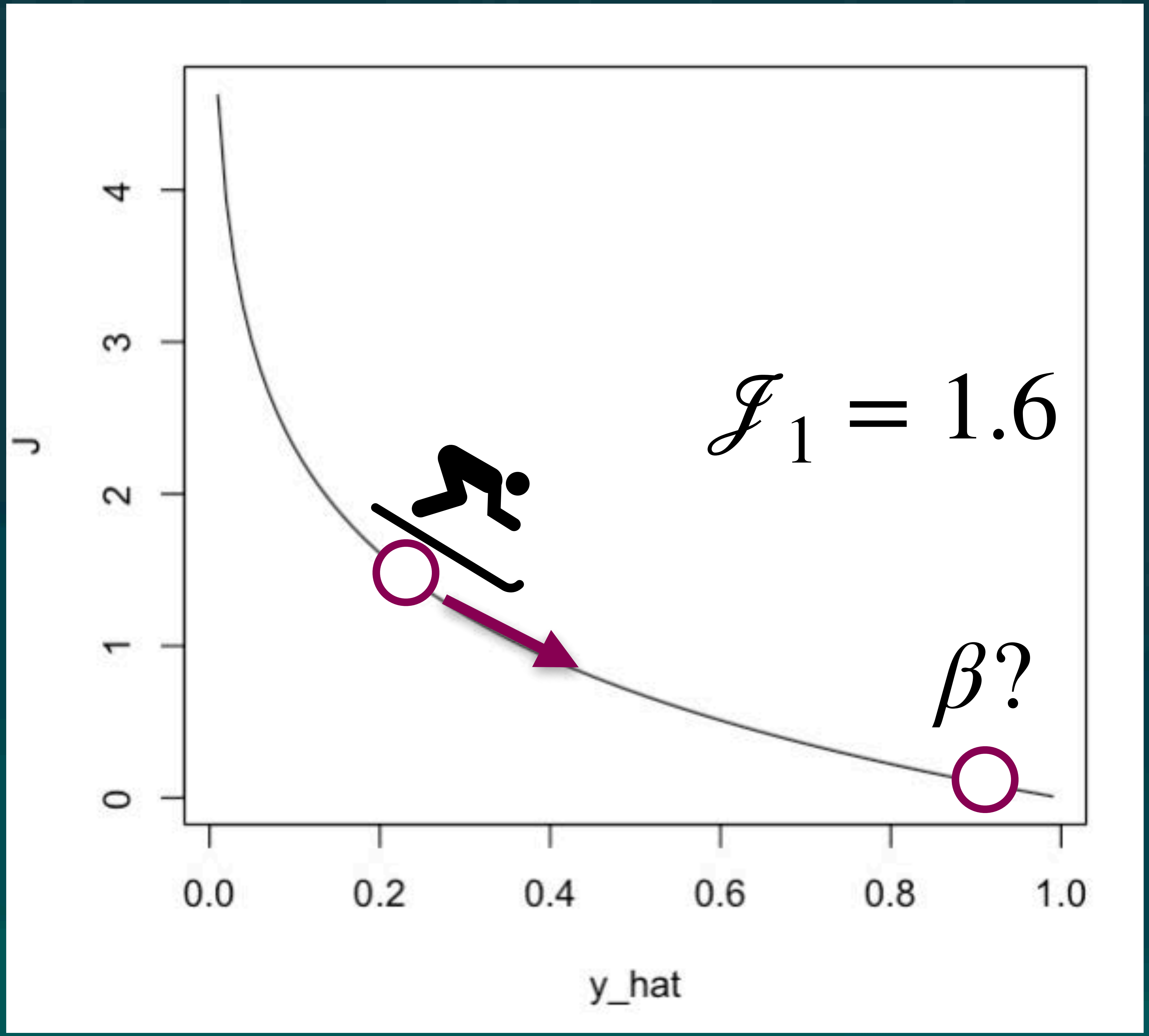
Cost function graph

How do we reduce the cost?

$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

$$\beta^T = [0\,0\,0\,0]$$

$$y_1 = 1,\ \hat{y}_1 = 0.2 \rightarrow \mathcal{J}_1 = 1.6$$



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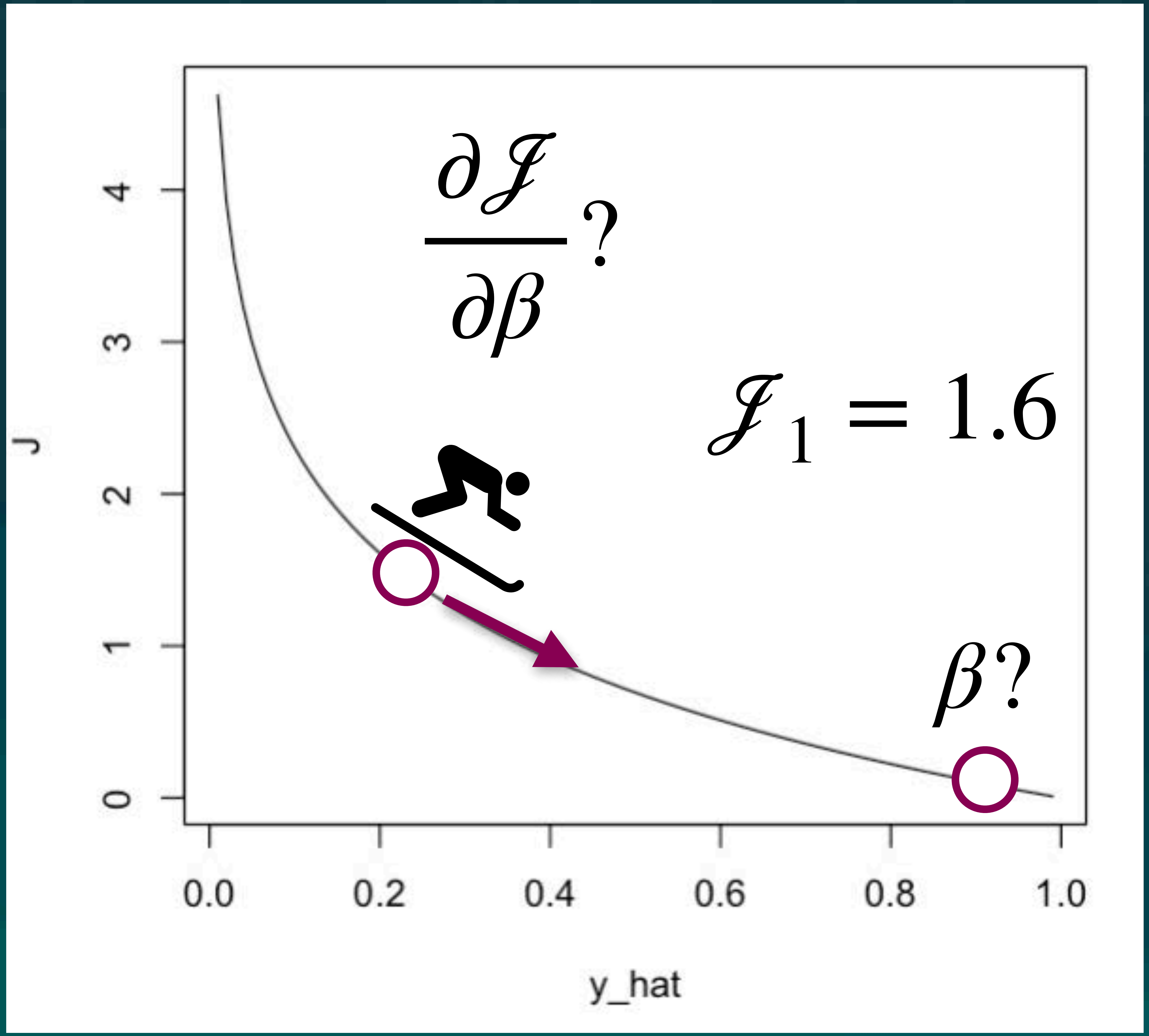

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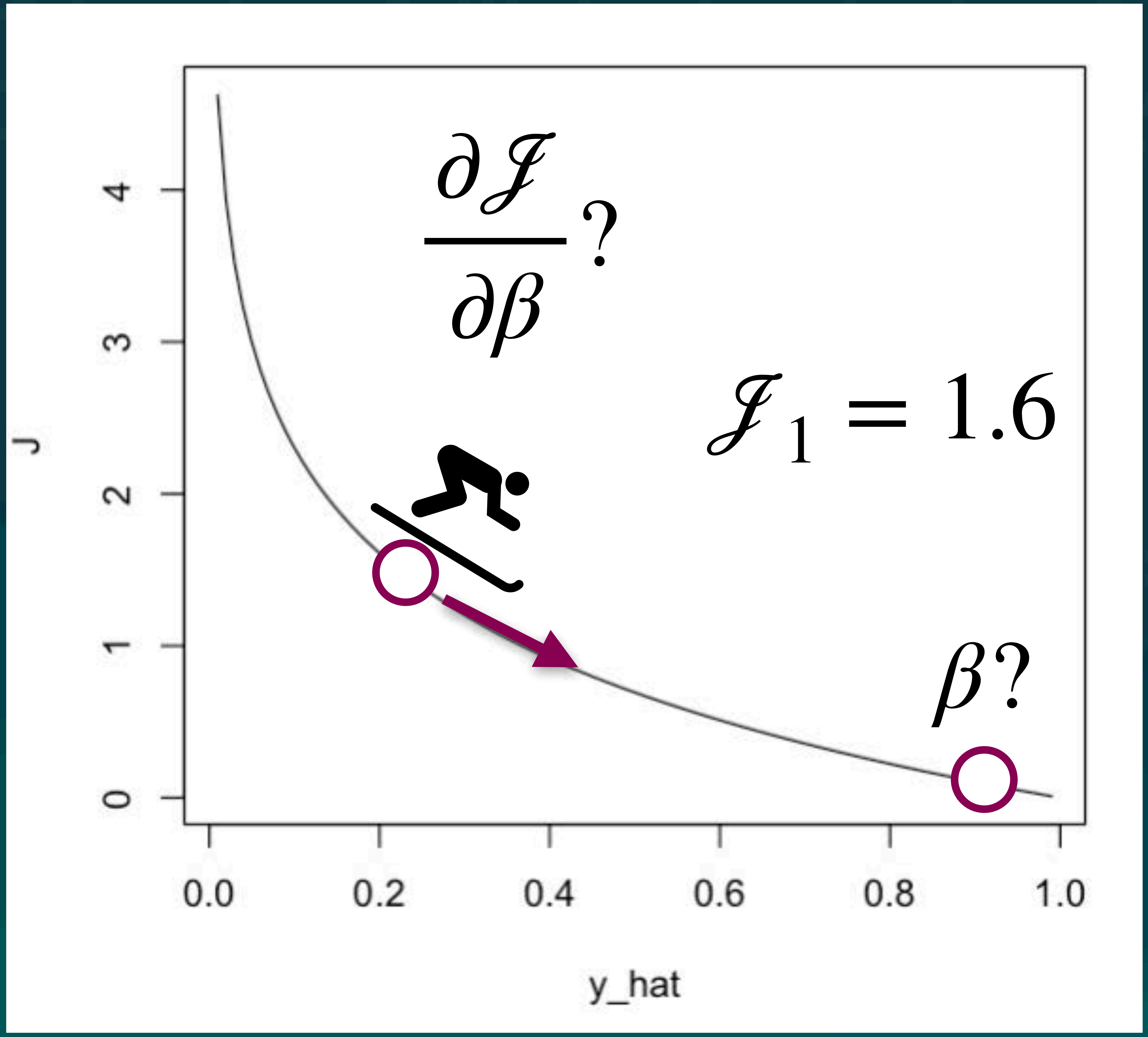
Derivative for patient 1: $\dfrac{\partial \mathcal{J}_1}{\partial \beta} = x_i(\hat{y}_i - y_i)$



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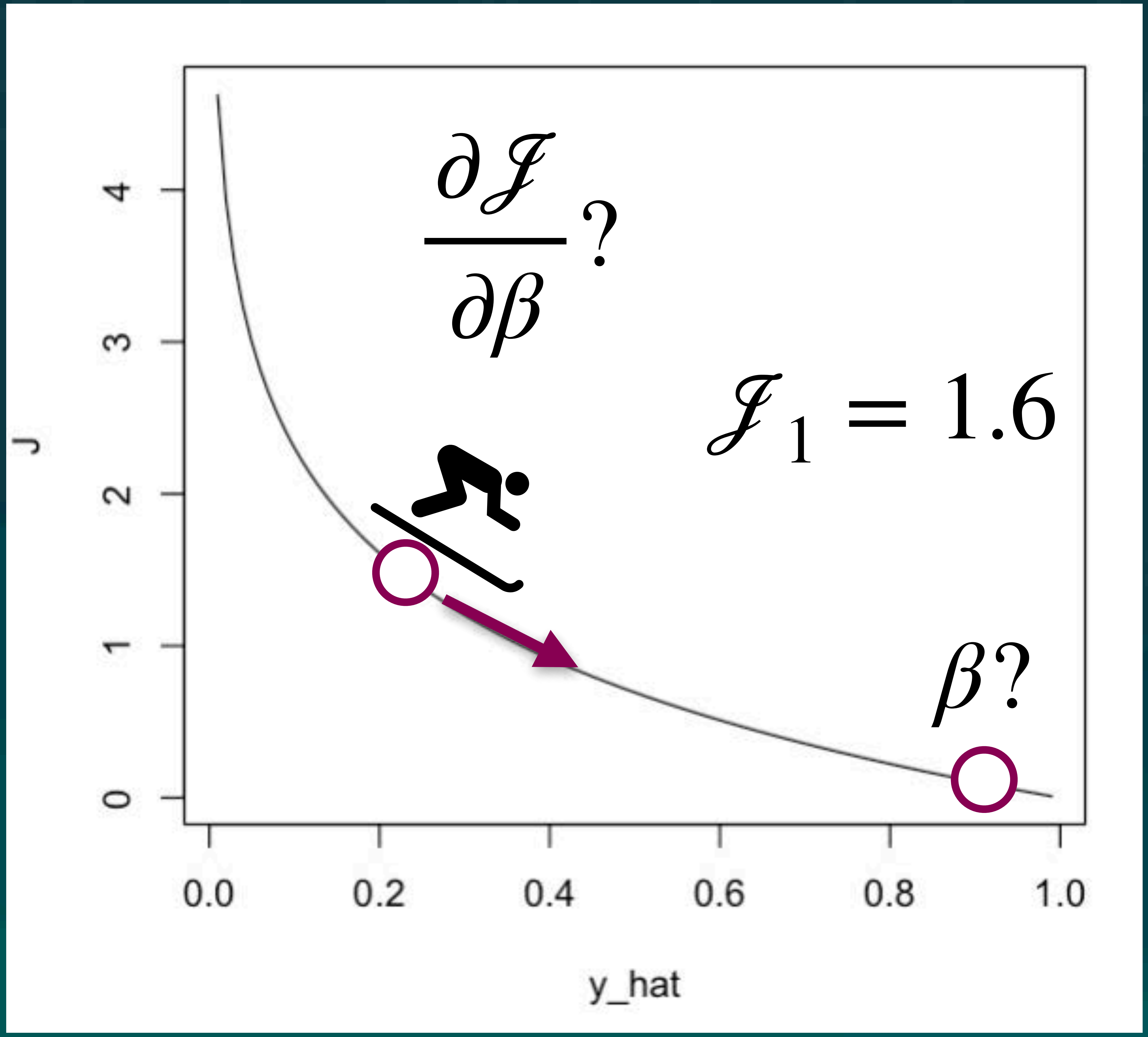
Derivative for patient 1: $\dfrac{\partial \mathcal{J}_1}{\partial \beta} = x_i(\hat{y}_i - y_i)$

Derivative across patients: $\dfrac{\partial \mathcal{J}}{\partial \beta} = \dfrac{1}{N} \sum_{i=1}^{N} x_i(\hat{y}_i - y_i)$



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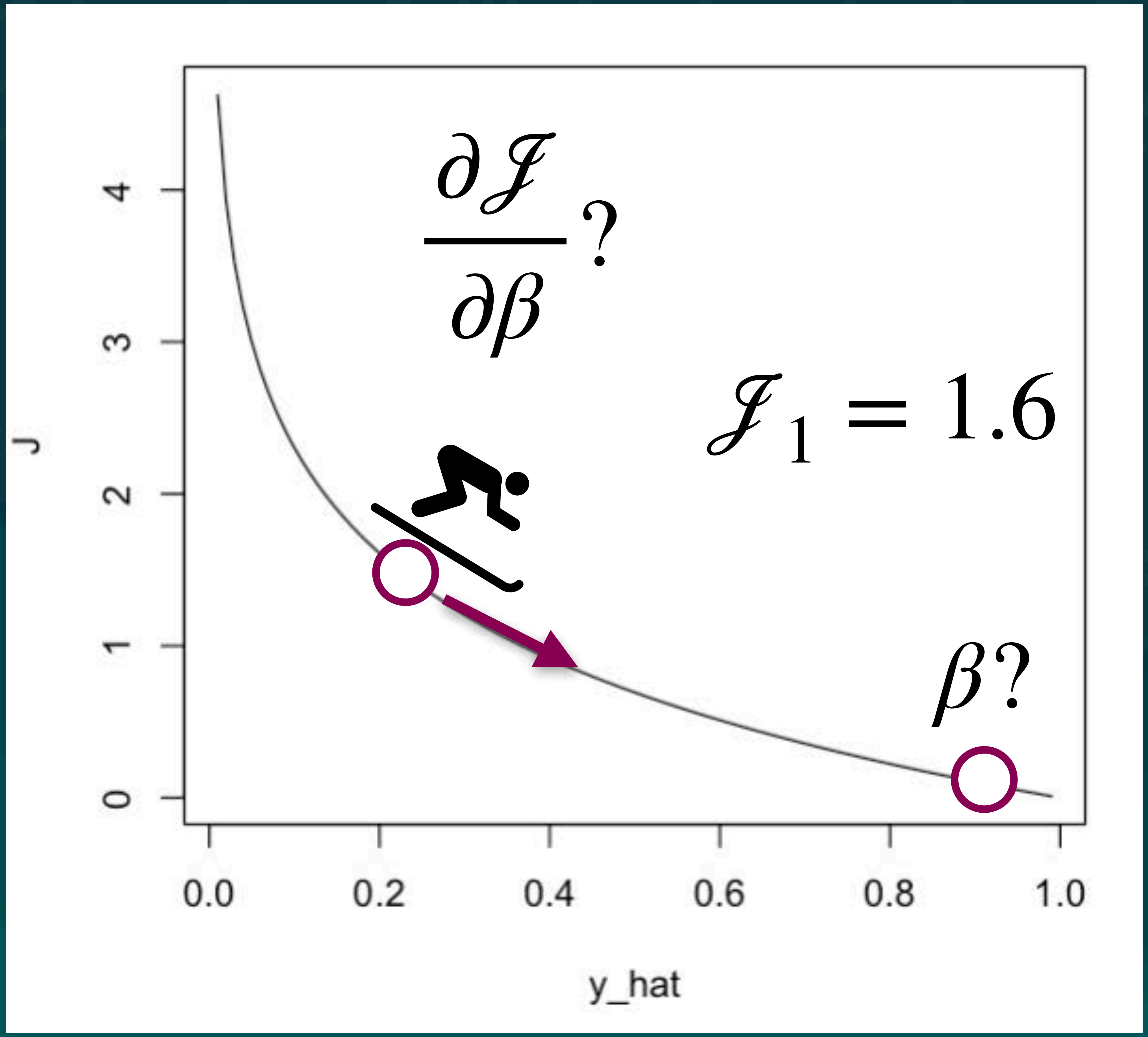
$$y_1 = 1,\ \hat{y}_1 = 0.2 \rightarrow \mathcal{J}_1 = 1.6$$

Update beta-estimates:

$$\frac{\partial \mathcal{J}}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N} x_i(\hat{y}_i - y_i) = \begin{pmatrix} 1.2 \\ 0.3 \\ 0.4 \\ 0.3 \end{pmatrix}$$



Cost function graph

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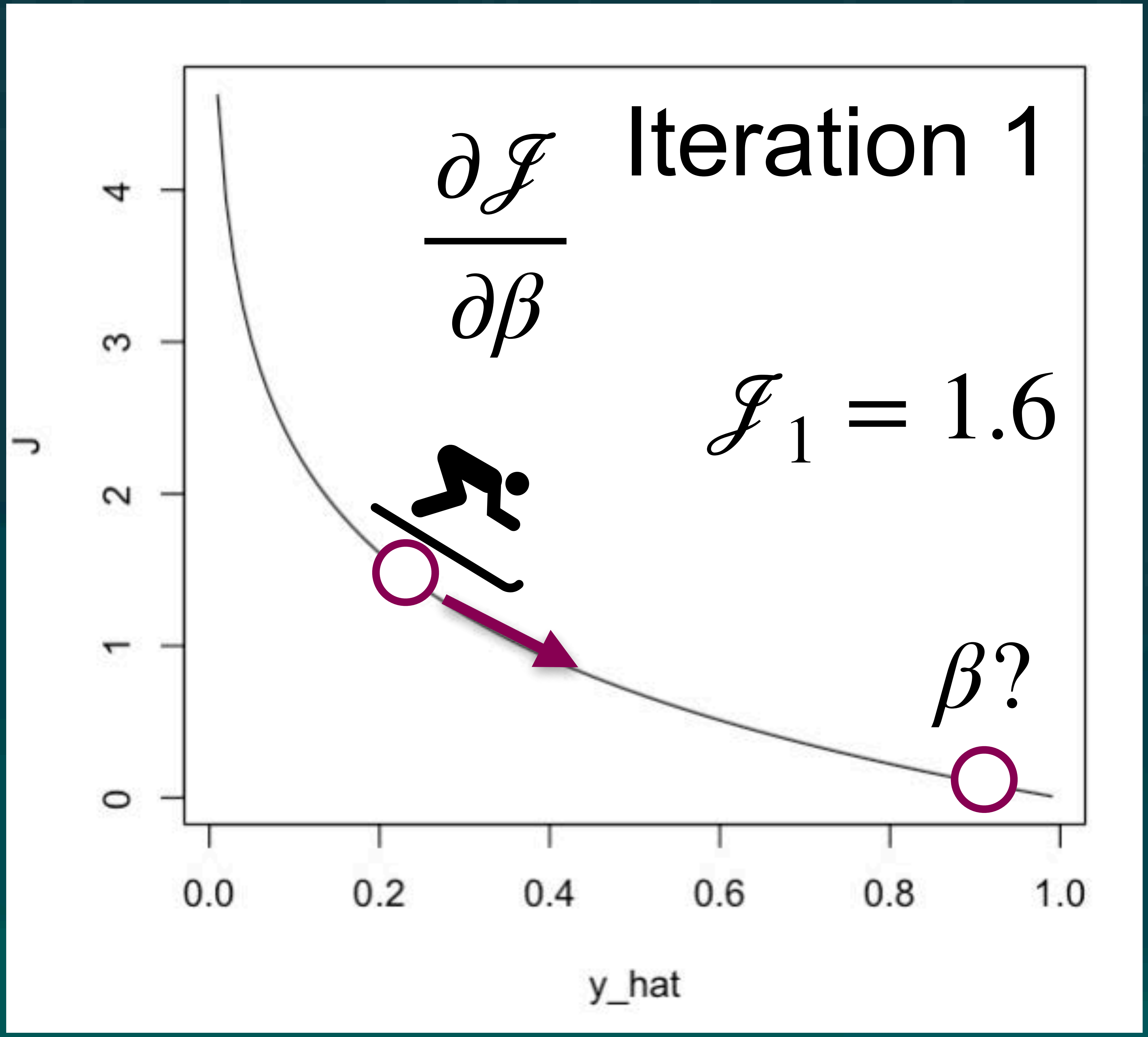
$$\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$

$$\alpha = 0.0001$$



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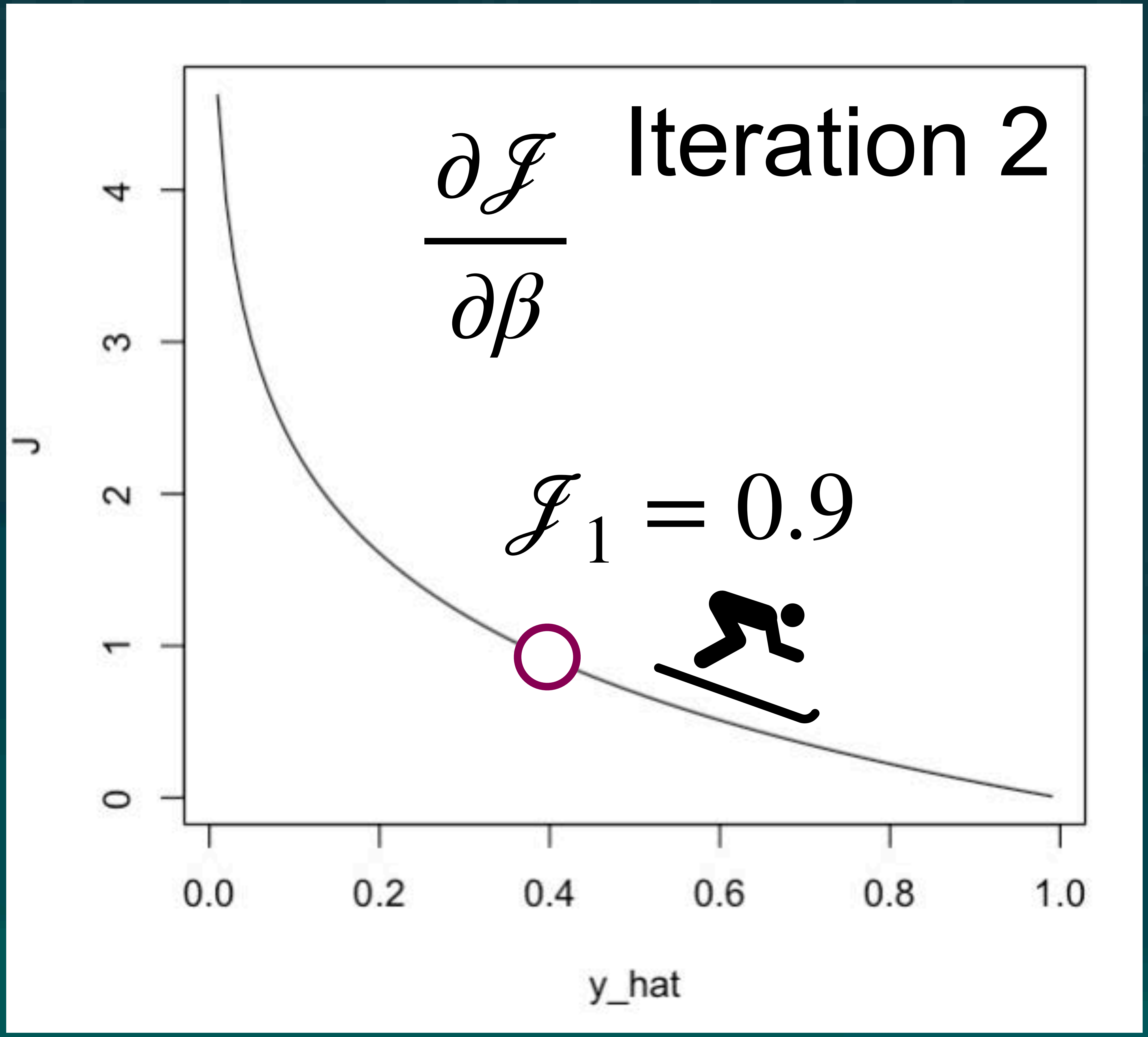
$$\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$

$$\alpha = 0.0001$$



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$$\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$

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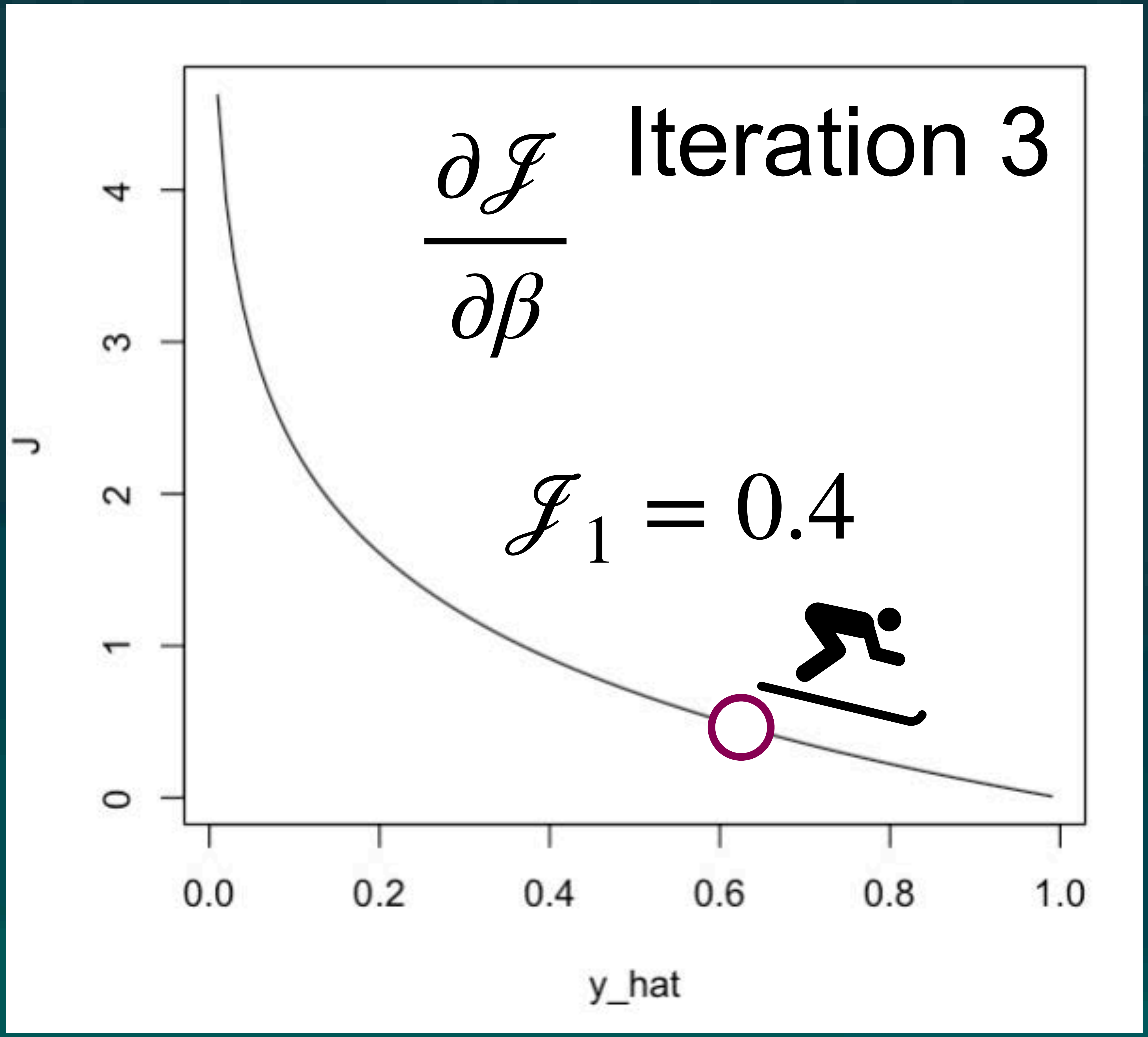

Cost function graph

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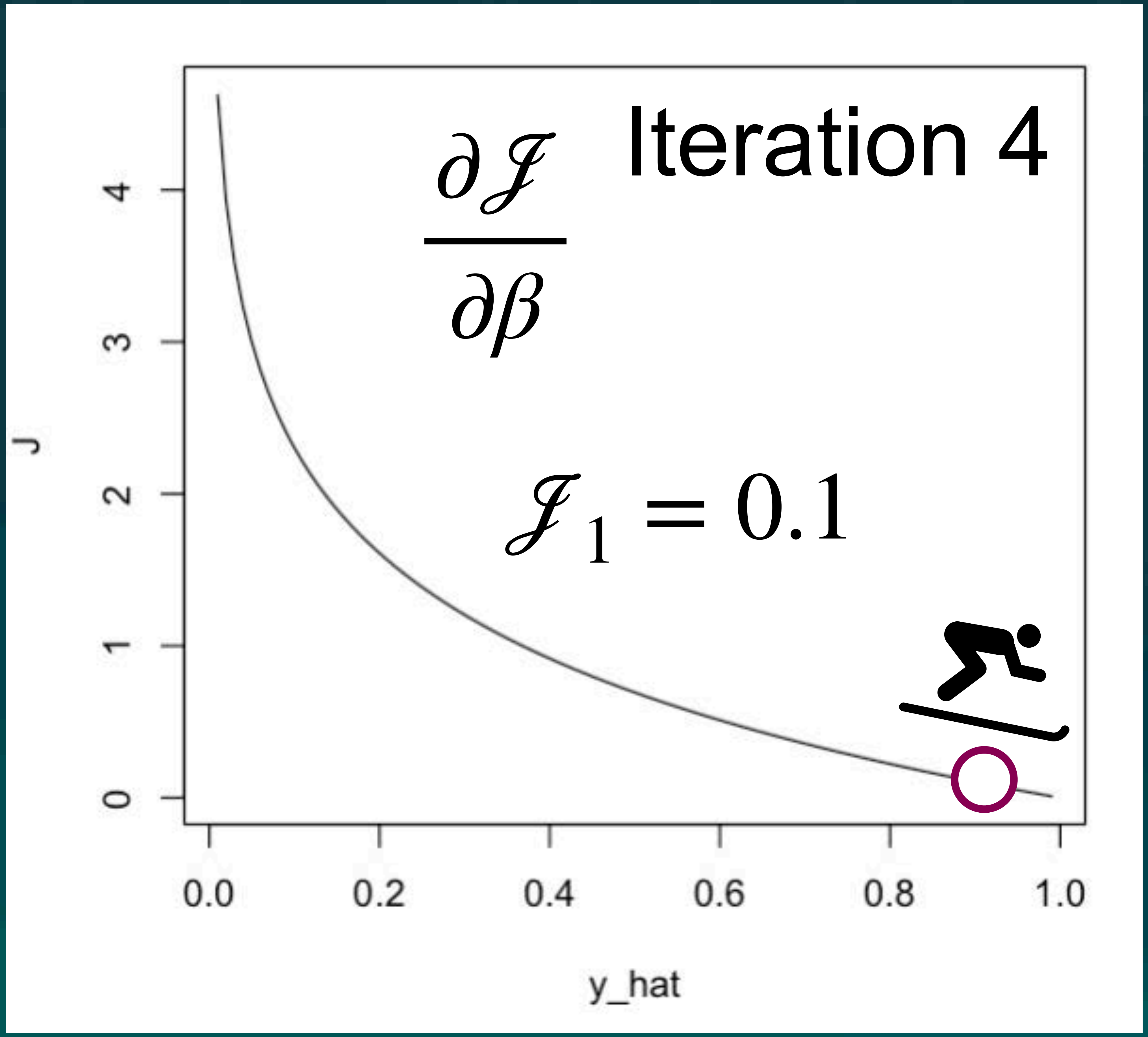
$$\mathcal{J}(\hat{y}, y) = \sum_{i=1}^{n} \mathcal{J}_i(\hat{y}_i, y_i)$$

$$\beta^T = [0\,0\,0\,0]$$

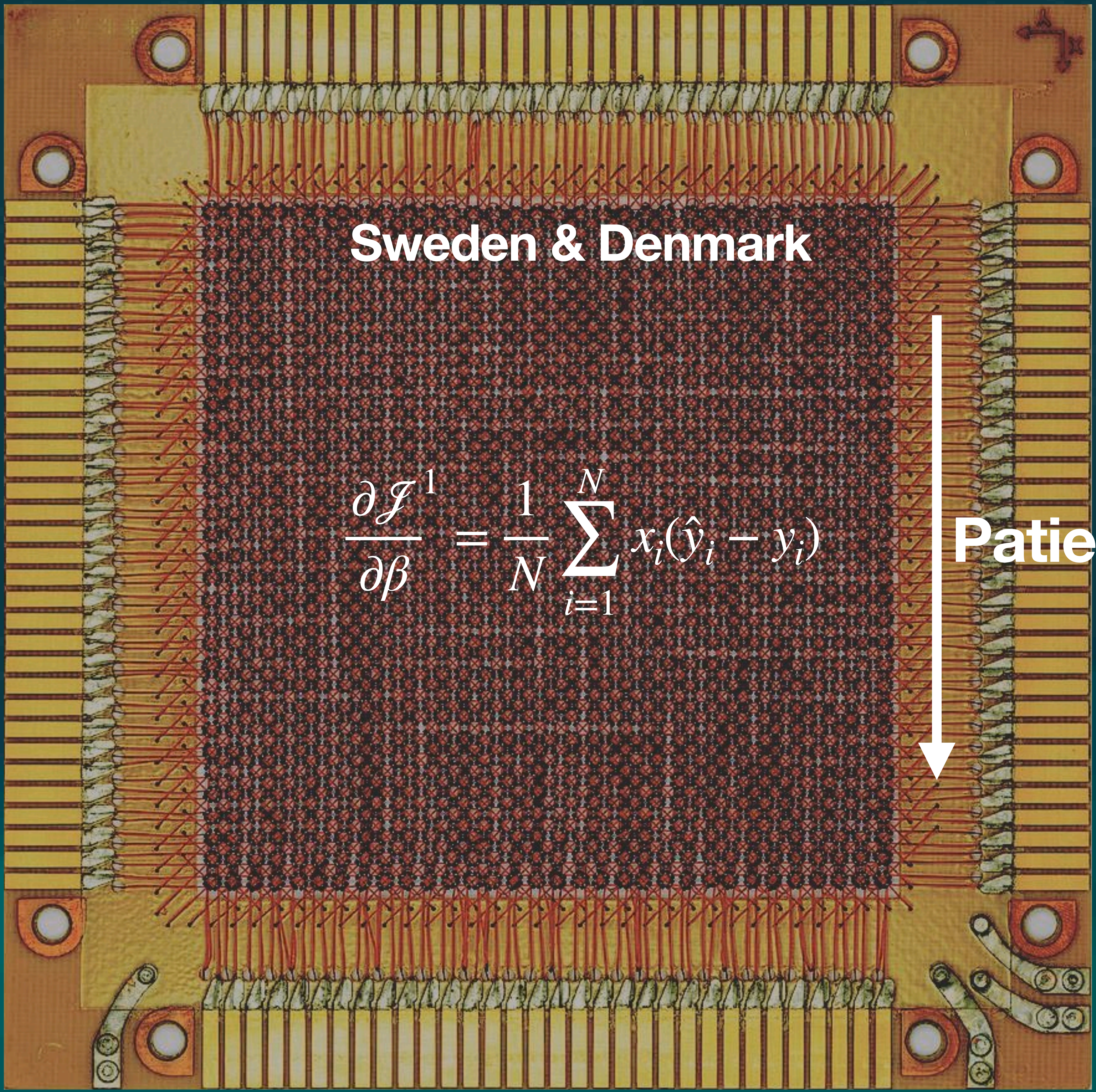
$$y_1 = 1,\ \hat{y}_1 = 0.2 \rightarrow \mathcal{J}_1 = 1.6$$

$$y_1 = 1,\ \hat{y}_1 = 0.9 \rightarrow \mathcal{J}_1 = 0.1$$

Final result: $\beta^T = [0.2\,0.3\,0.4\,0.2]$



Cost function graph



Sweden & Denmark

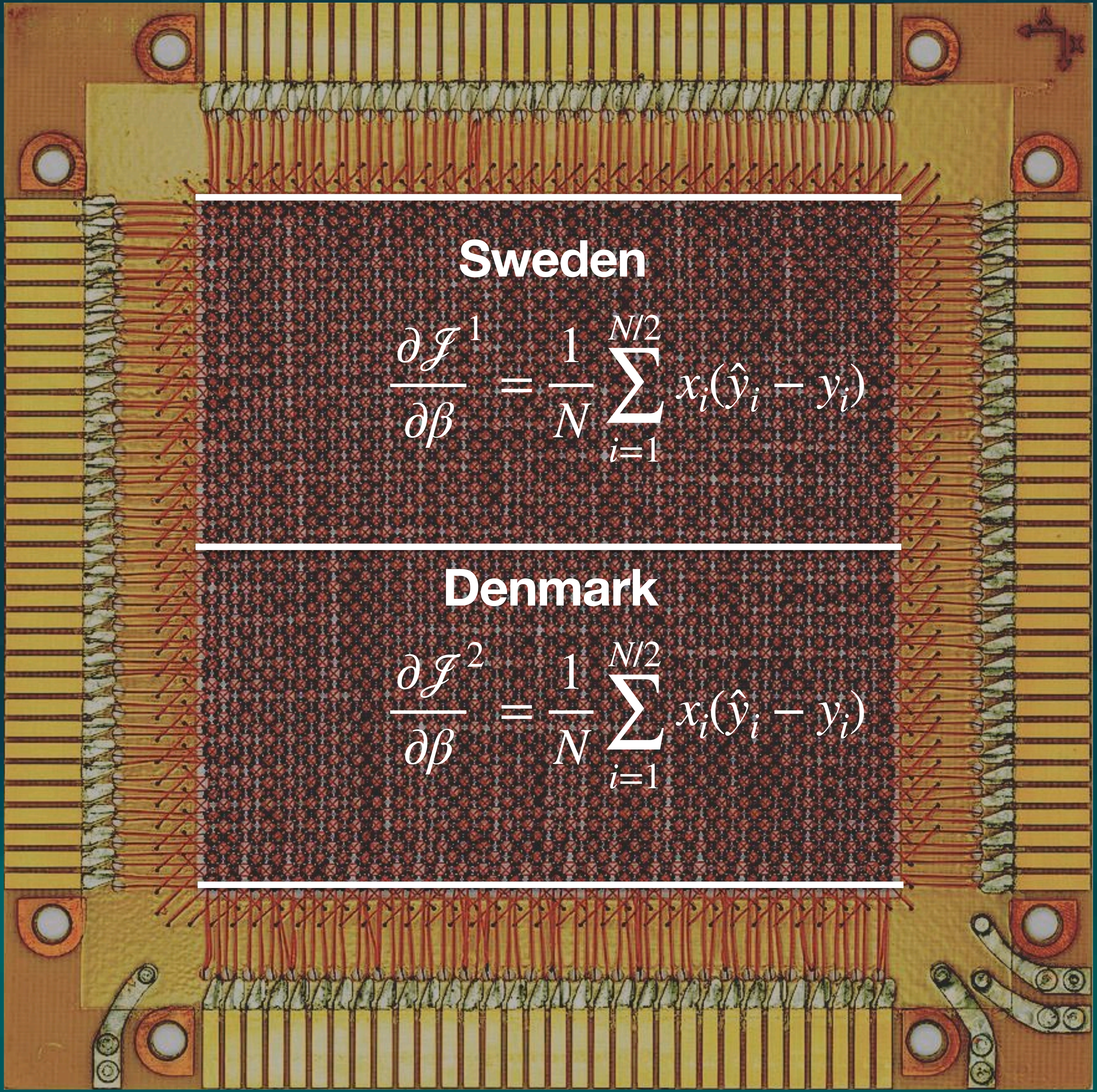
$$\frac{\partial \mathcal{J}^1}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N} x_i(\hat{y}_i - y_i)$$

Patients

N=total number of patients

If data was merged, we could run the sum across all patients and then update the beta-estimates:

Update: $\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$



Sweden

$$\frac{\partial \mathcal{J}^{1}}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N/2} x_i(\hat{y}_i - y_i)$$

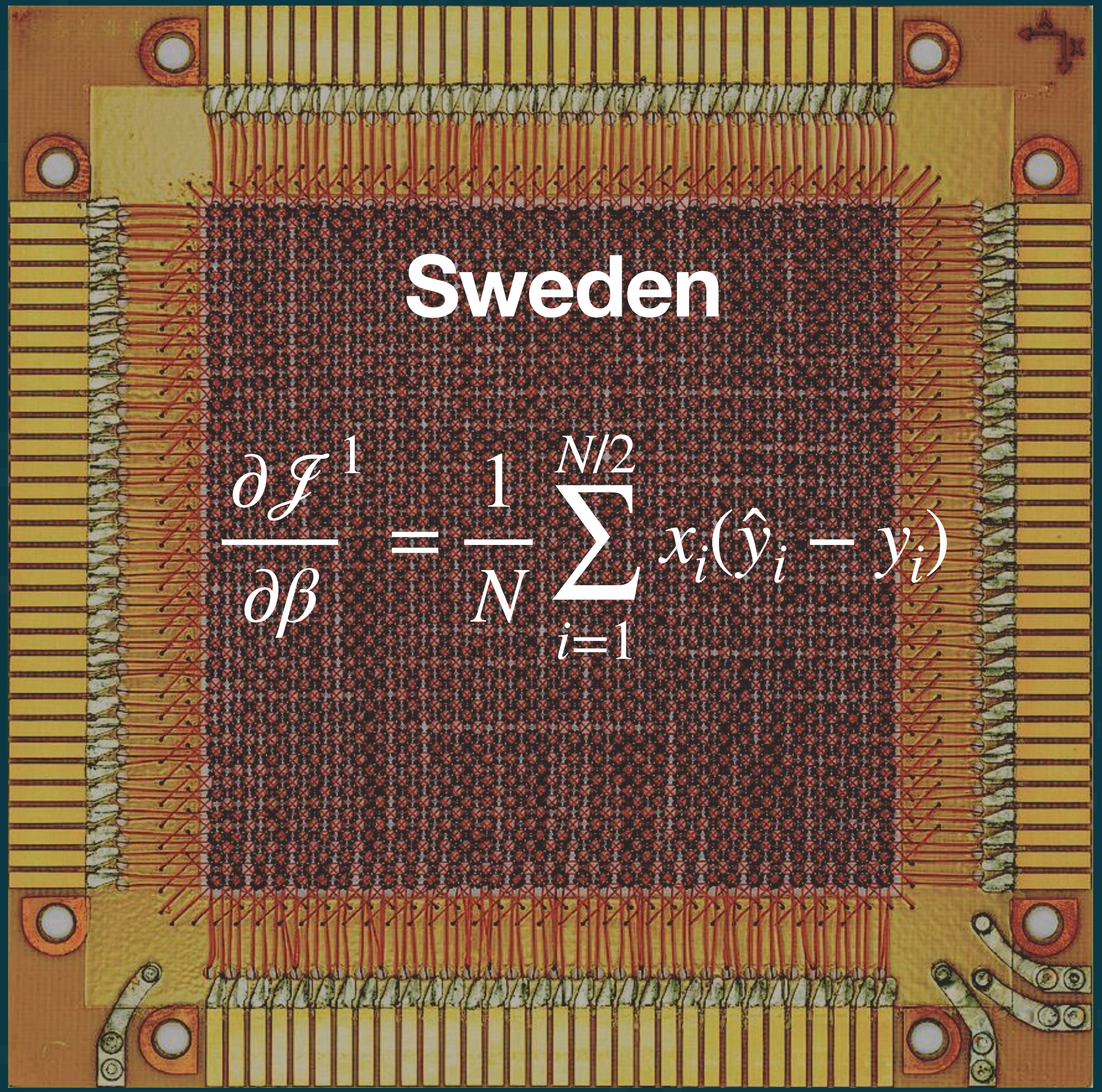
Denmark

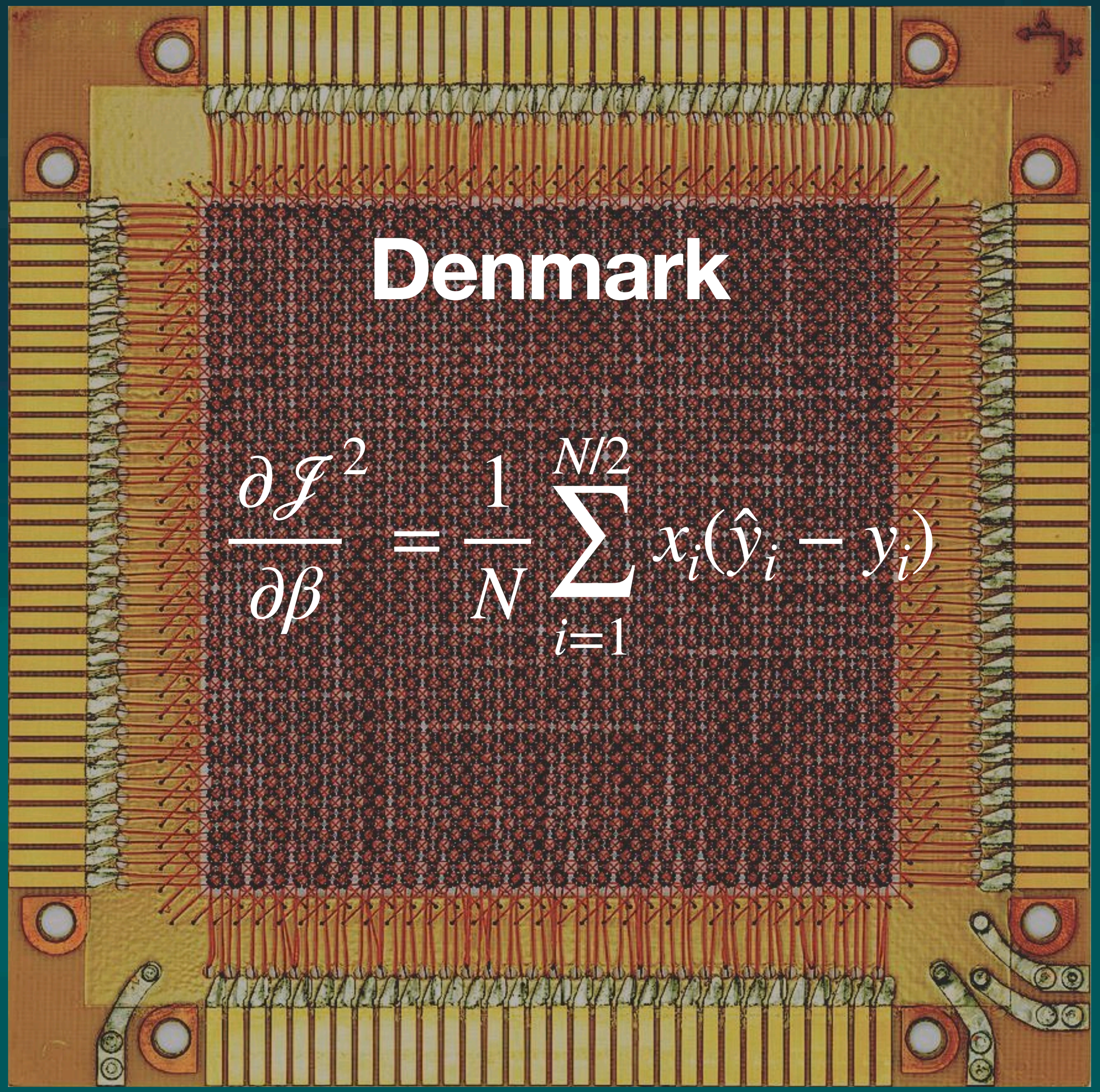
$$\frac{\partial \mathcal{J}^{2}}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N/2} x_i(\hat{y}_i - y_i)$$

N=total number of patients

Since the change in beta is a sum across patients, we can also calculate the sum for each registry and merge the sums to get the total result.

$$\frac{\partial \mathcal{J}}{\partial \beta} = \left(\frac{\partial \mathcal{J}^{1}}{\partial \beta} + \frac{\partial \mathcal{J}^{2}}{\partial \beta}\right) \qquad \beta := \beta - \alpha\frac{\partial \mathcal{J}}{\partial \beta}$$

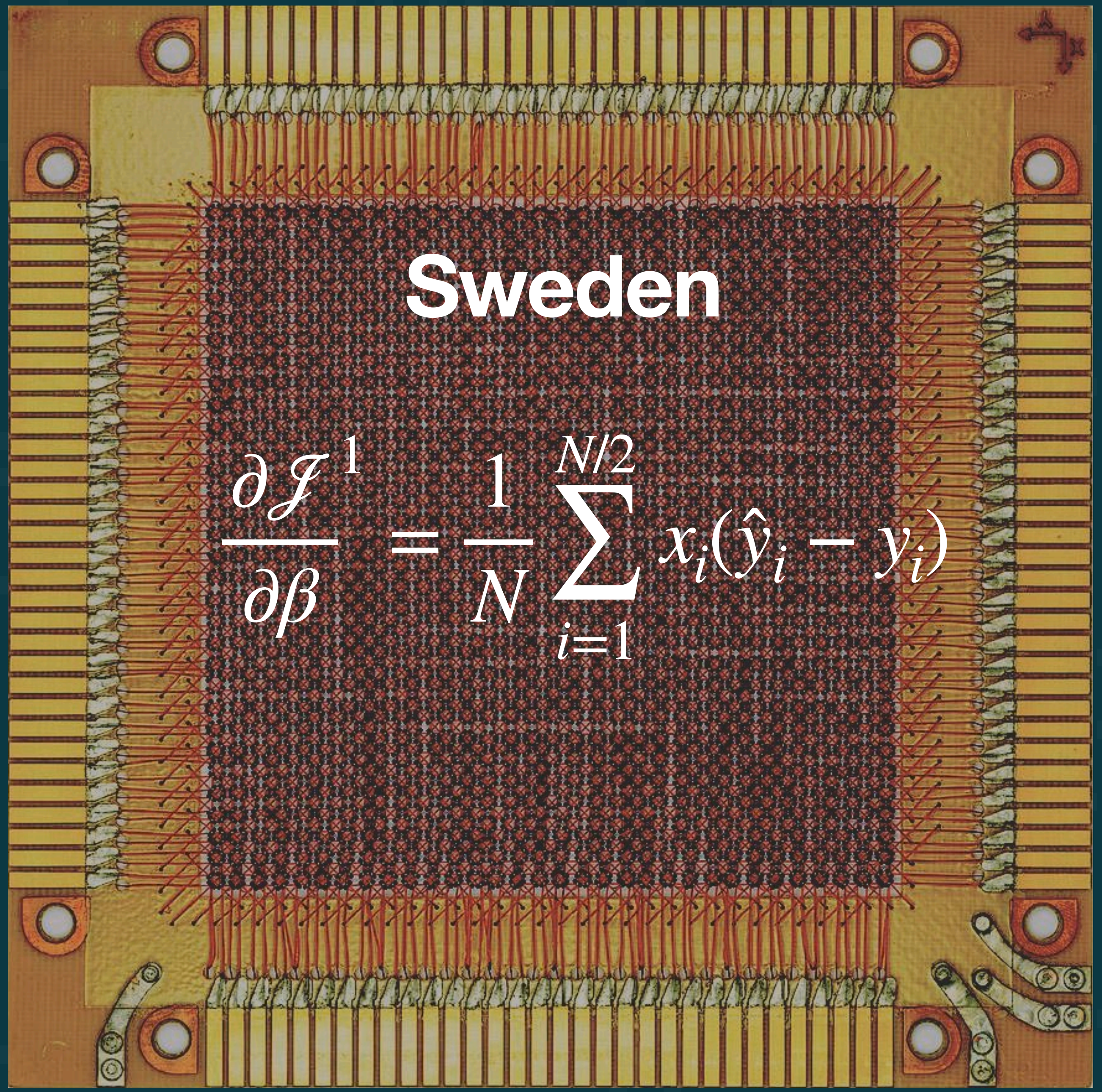


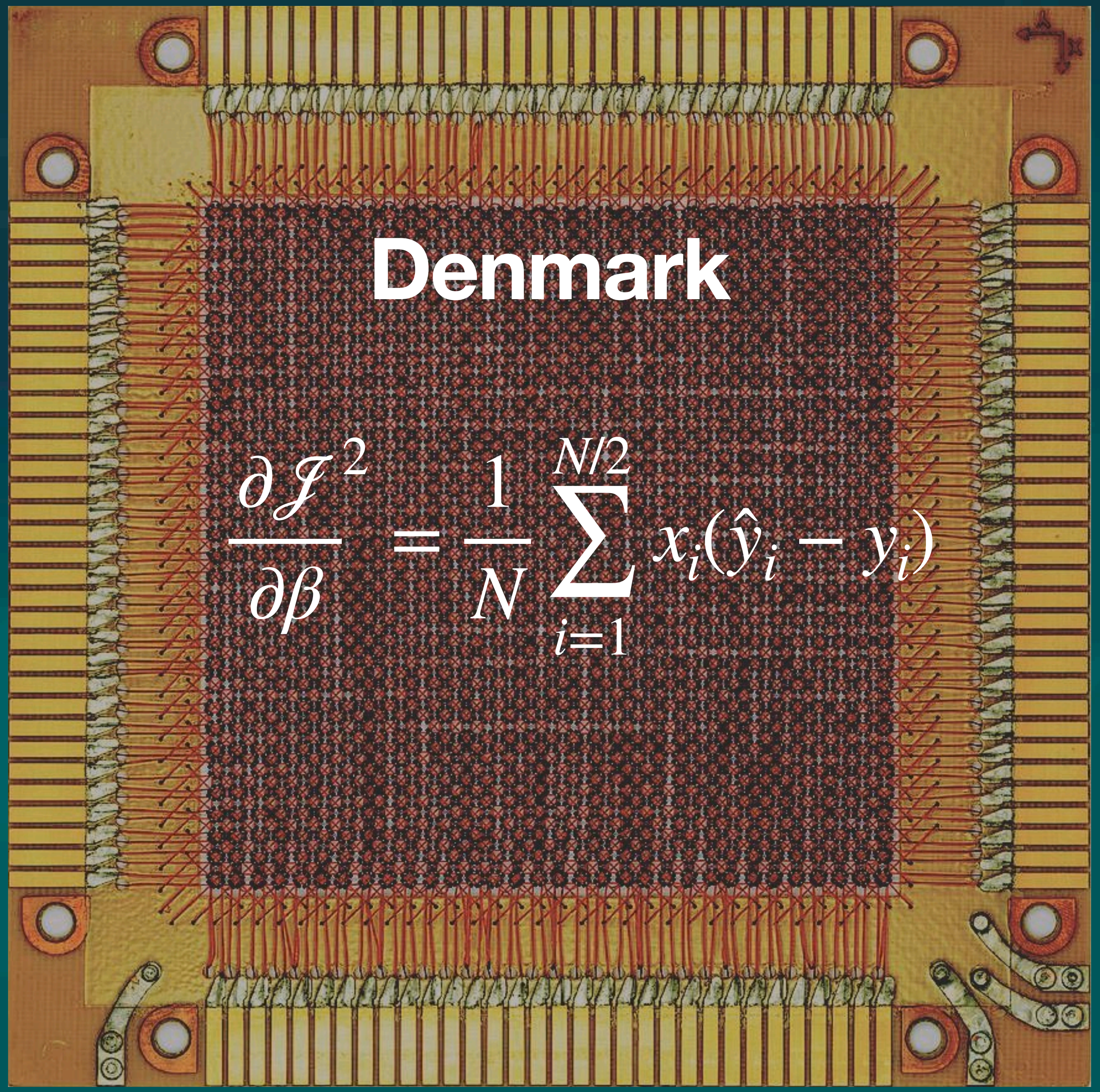


Central computer

N=total number of patients

$$\frac{\partial \mathcal{J}}{\partial \beta} = \left(\frac{\partial \mathcal{J}^1}{\partial \beta} + \frac{\partial \mathcal{J}^2}{\partial \beta}\right) \qquad \beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$





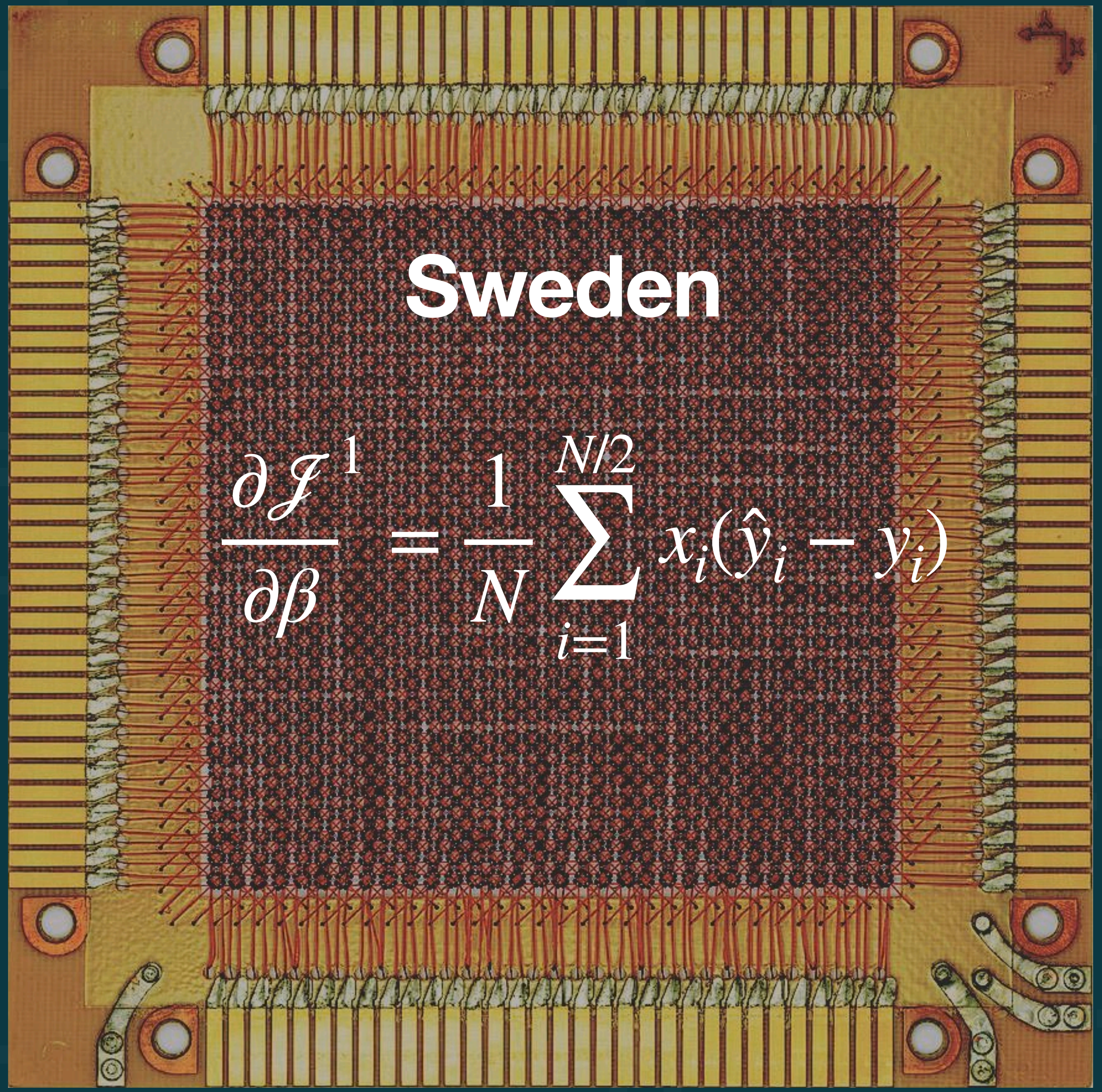
Central computer

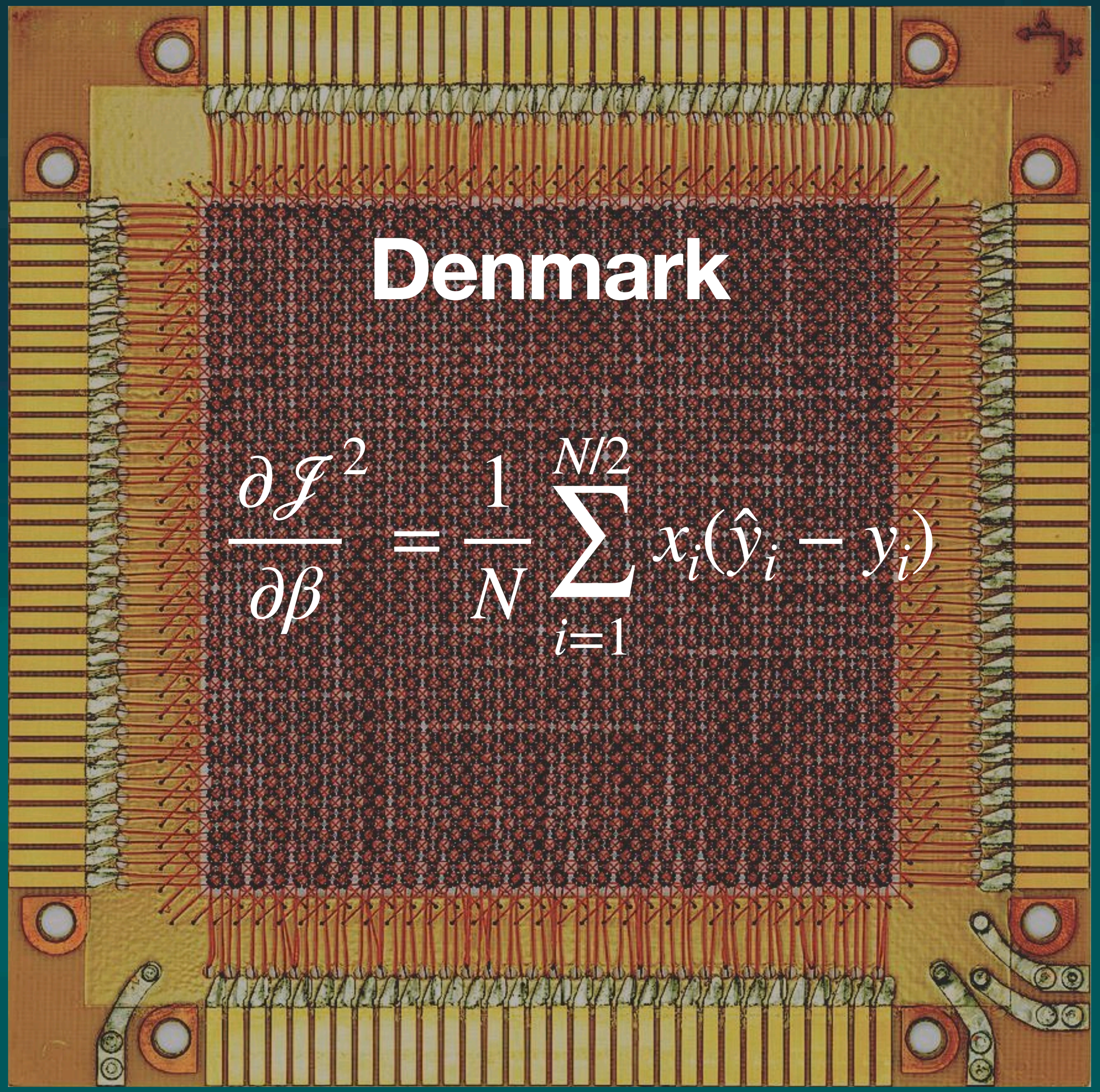
N=total number of patients

$$\frac{\partial \mathcal{J}^1}{\partial \beta} = \begin{pmatrix} 0.2 \\ 0.5 \\ 1.0 \\ 2.0 \end{pmatrix}$$

$$\frac{\partial \mathcal{J}^2}{\partial \beta} = \begin{pmatrix} 0.3 \\ 0.2 \\ 0.5 \\ 1.0 \end{pmatrix}$$

$$\frac{\partial \mathcal{J}}{\partial \beta} = (\frac{\partial \mathcal{J}^1}{\partial \beta} + \frac{\partial \mathcal{J}^2}{\partial \beta}) \qquad \beta := \beta - \alpha\frac{\partial \mathcal{J}}{\partial \beta}$$





Central computer

N=total number of patients

$$\beta = \begin{pmatrix} 1.5 \\ 0.2 \\ 0.2 \\ 0.5 \end{pmatrix}$$

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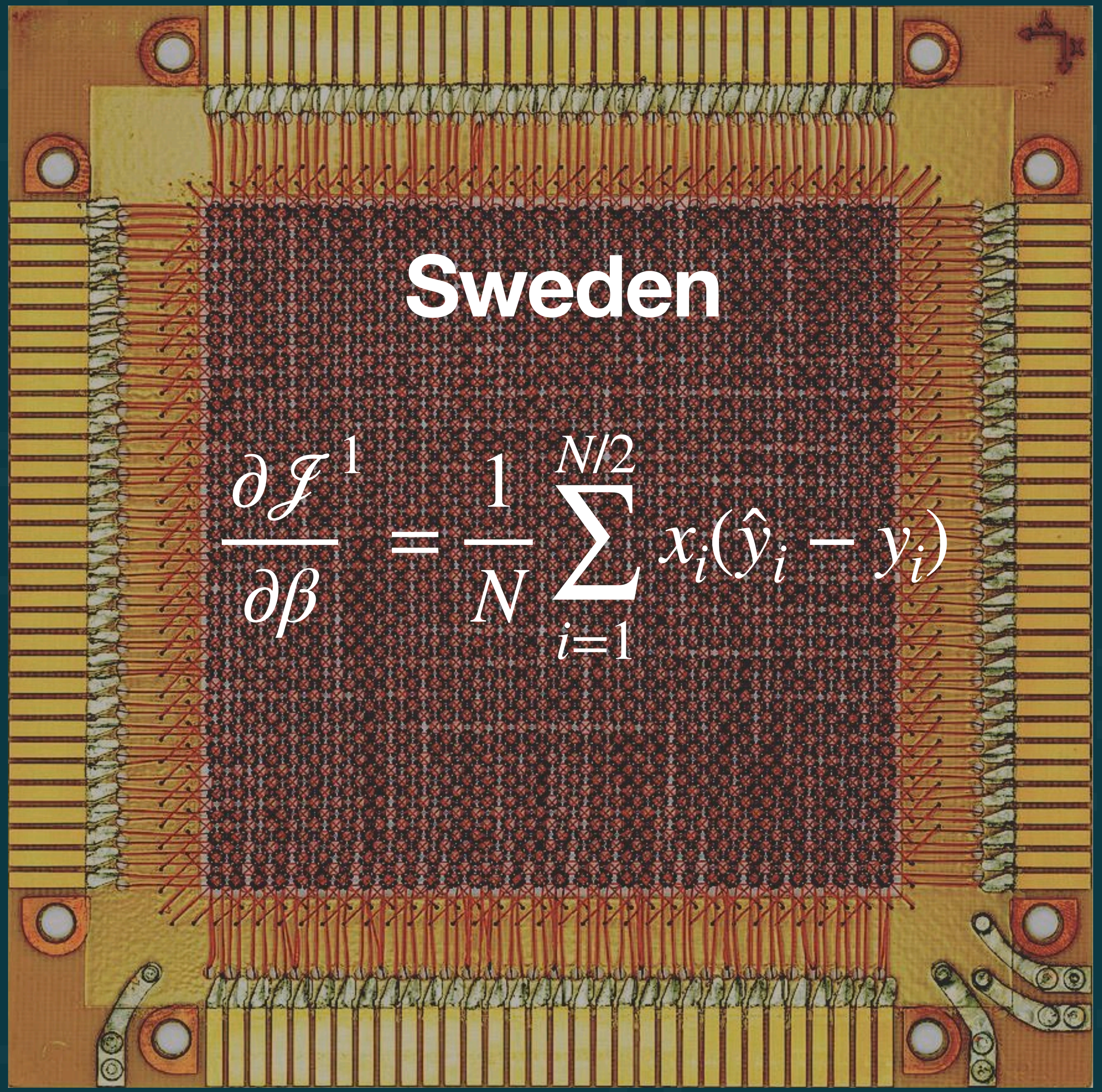
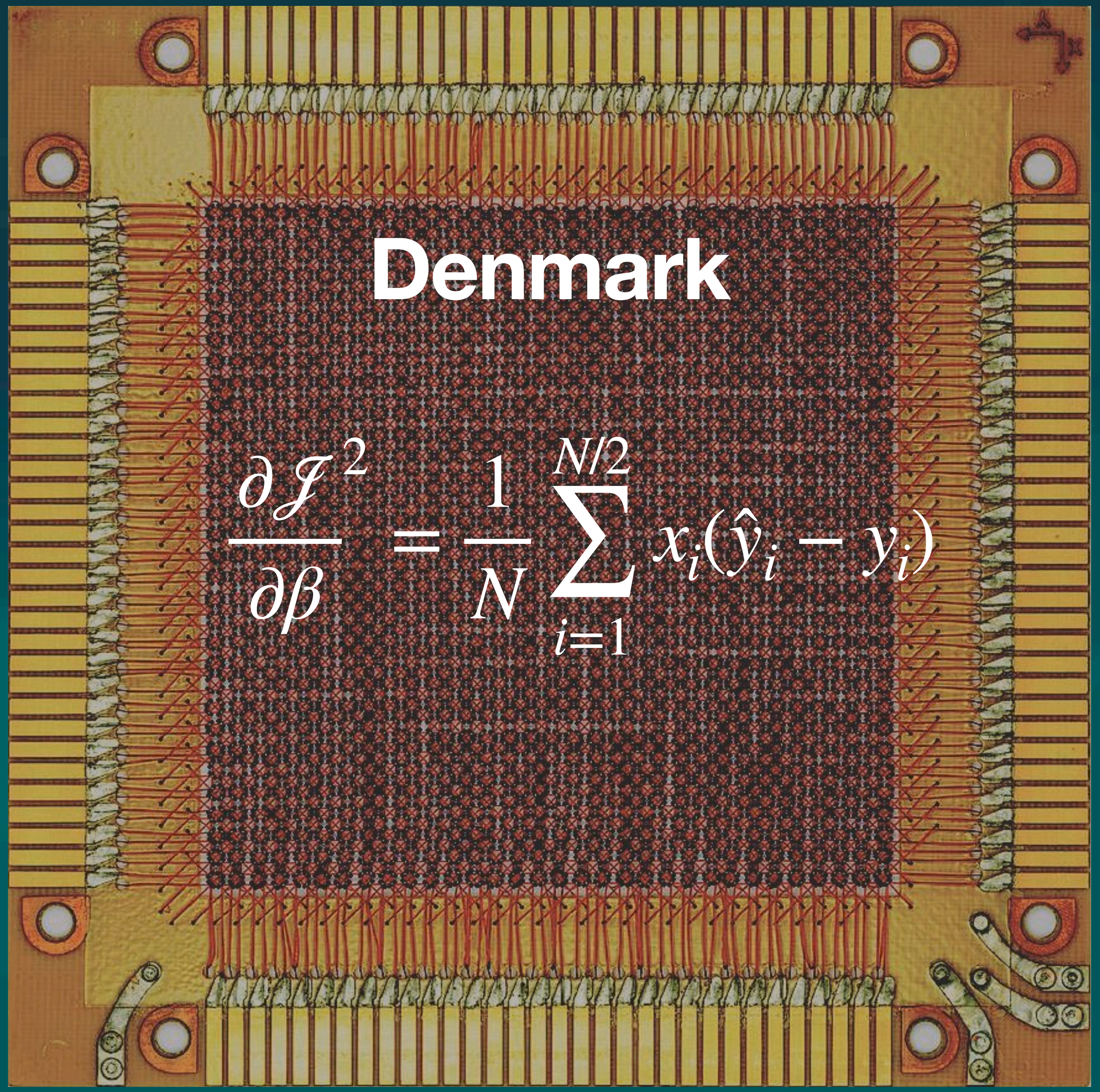
$$\frac{\partial \mathcal{J}}{\partial \beta} = (\frac{\partial \mathcal{J}^1}{\partial \beta} + \frac{\partial \mathcal{J}^2}{\partial \beta}) \qquad \beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$



$$\frac{\partial \mathcal{J}^1}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N/2} x_i(\hat{y}_i - y_i)$$



$$\frac{\partial \mathcal{J}^2}{\partial \beta} = \frac{1}{N}\sum_{i=1}^{N/2} x_i(\hat{y}_i - y_i)$$

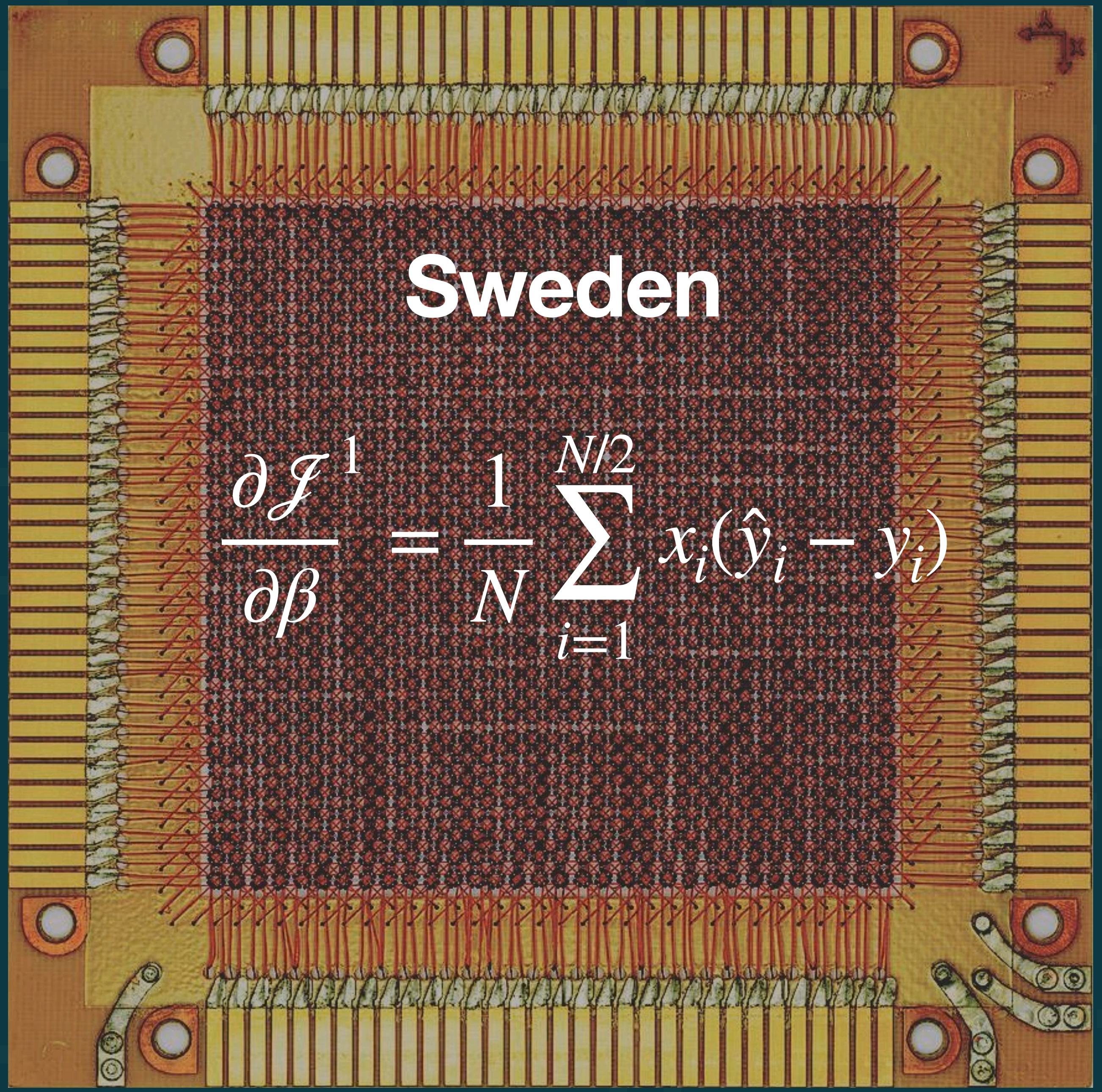
N=total number of patients

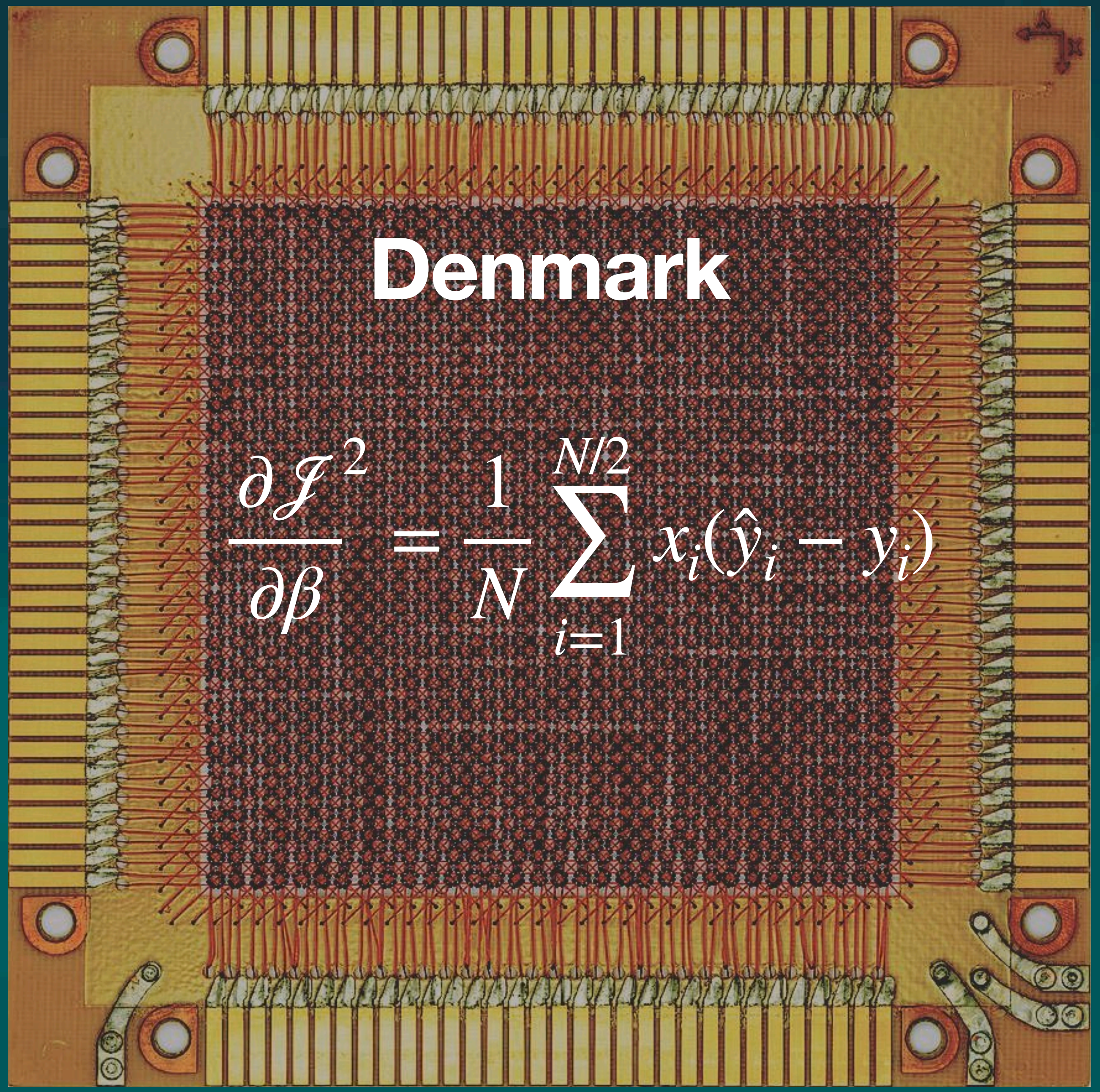
$$\frac{\partial \mathcal{J}^1}{\partial \beta} = \begin{pmatrix} 0.3 \\ 0.4 \\ 1.2 \\ 1.9 \end{pmatrix}$$

$$\frac{\partial \mathcal{J}^2}{\partial \beta} = \begin{pmatrix} 0.2 \\ 0.3 \\ 0.4 \\ 1.1 \end{pmatrix}$$

Central computer

$$\frac{\partial \mathcal{J}}{\partial \beta} = \left(\frac{\partial \mathcal{J}^1}{\partial \beta} + \frac{\partial \mathcal{J}^2}{\partial \beta}\right) \qquad \beta := \beta - \alpha\frac{\partial \mathcal{J}}{\partial \beta}$$





Central computer

N=total number of patients

$$\beta = \begin{pmatrix} 1.3 \\ 0.1 \\ 0.1 \\ 0.6 \end{pmatrix}$$

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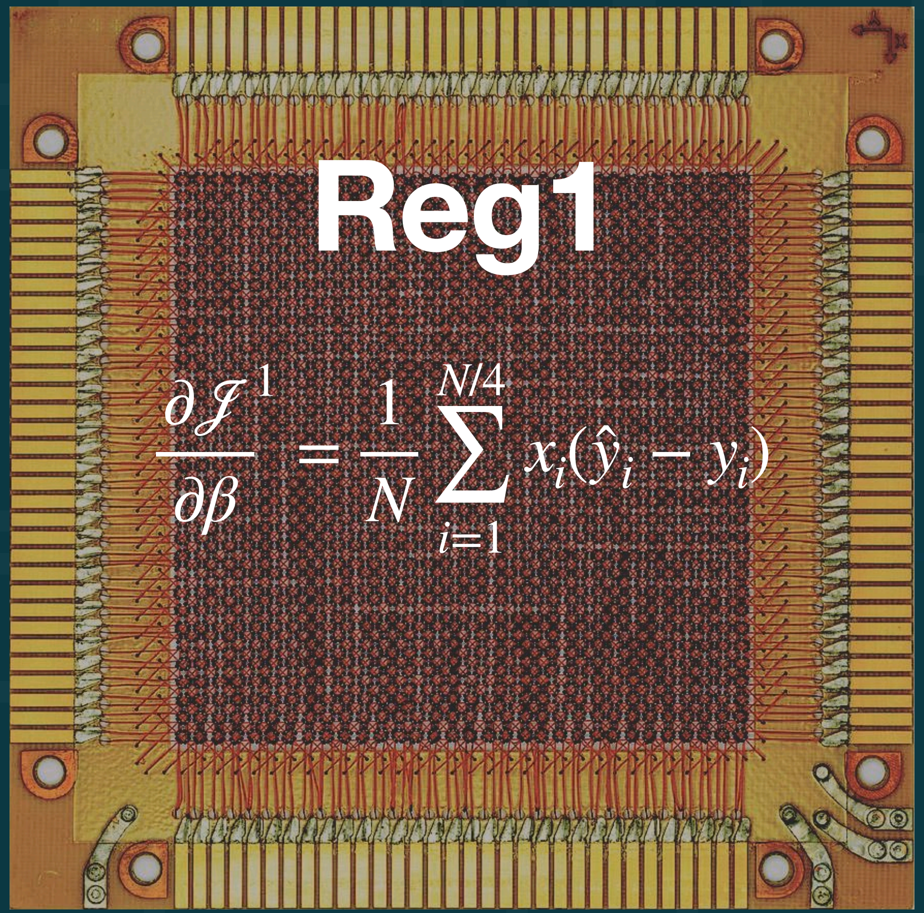

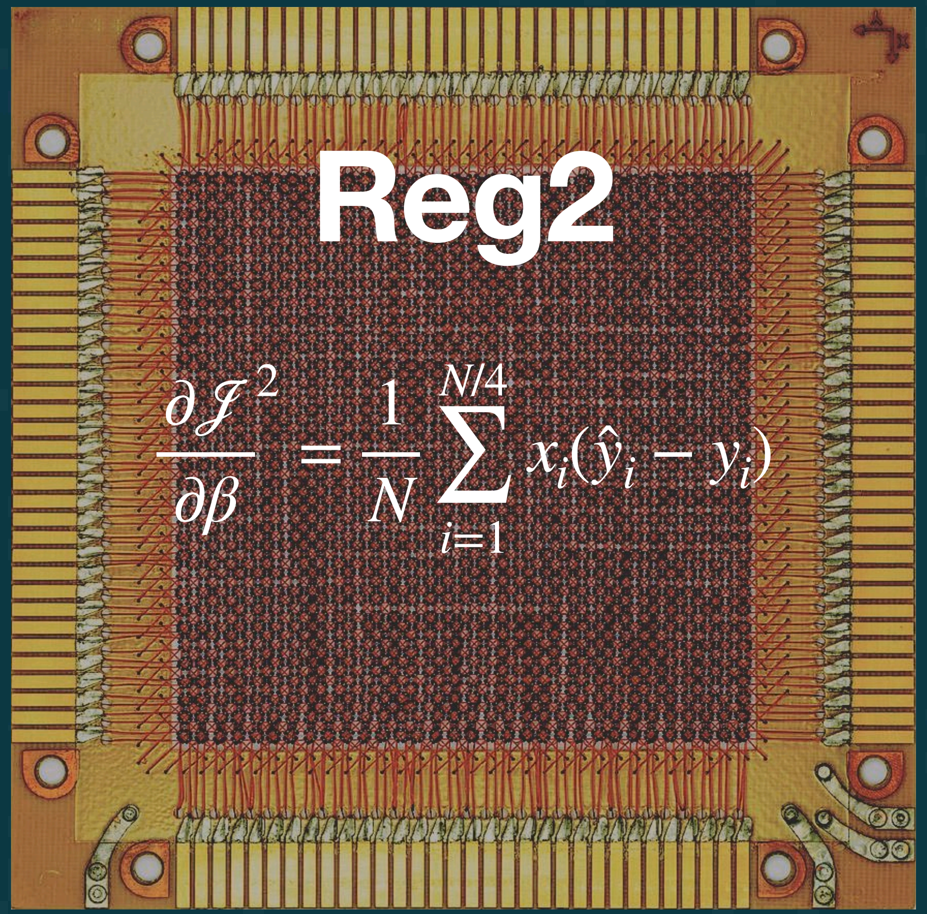

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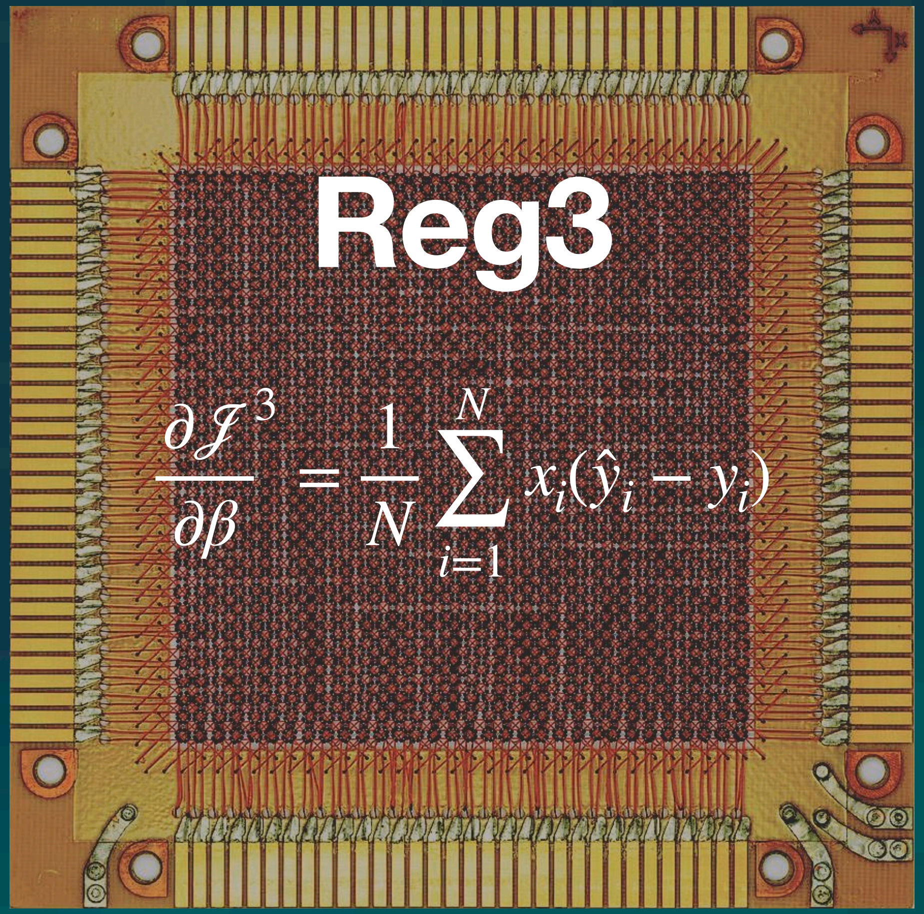
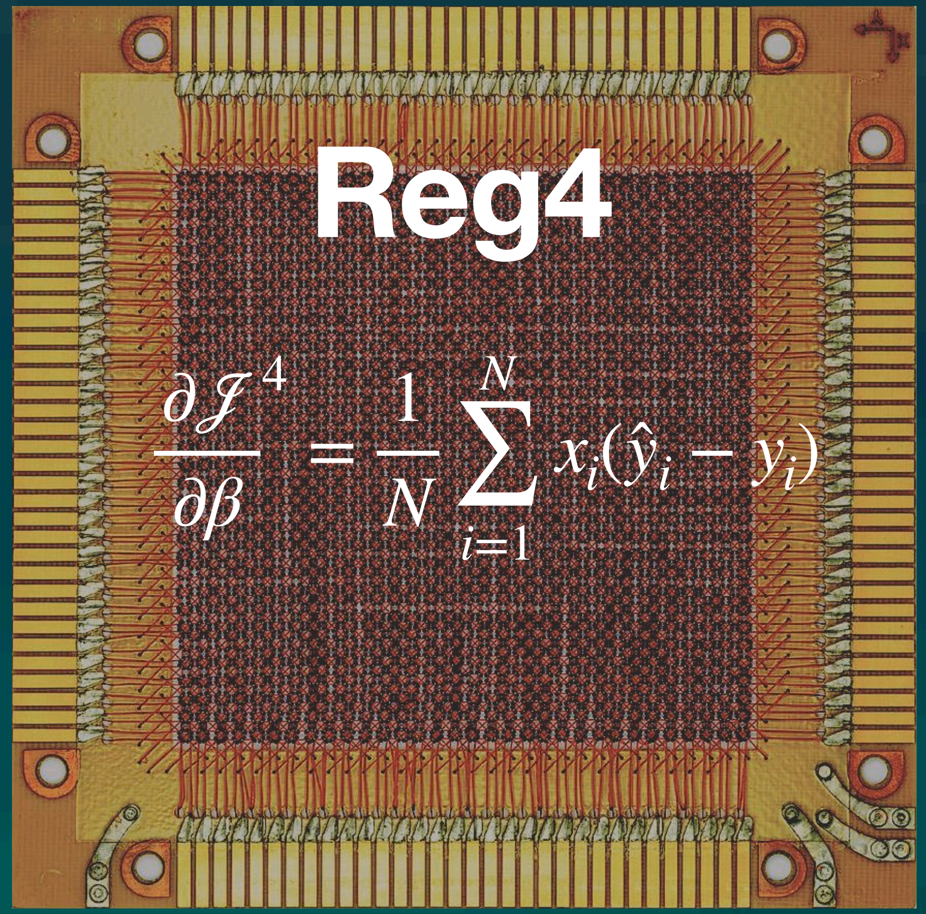




Total result across registries:

$$\frac{\partial \mathcal{J}}{\partial \beta} = \left(\frac{\partial \mathcal{J}^1}{\partial \beta} + \frac{\partial \mathcal{J}^2}{\partial \beta} + \frac{\partial \mathcal{J}^3}{\partial \beta} + \frac{\partial \mathcal{J}^4}{\partial \beta}\right)$$

Update: $\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$

Logistic regression

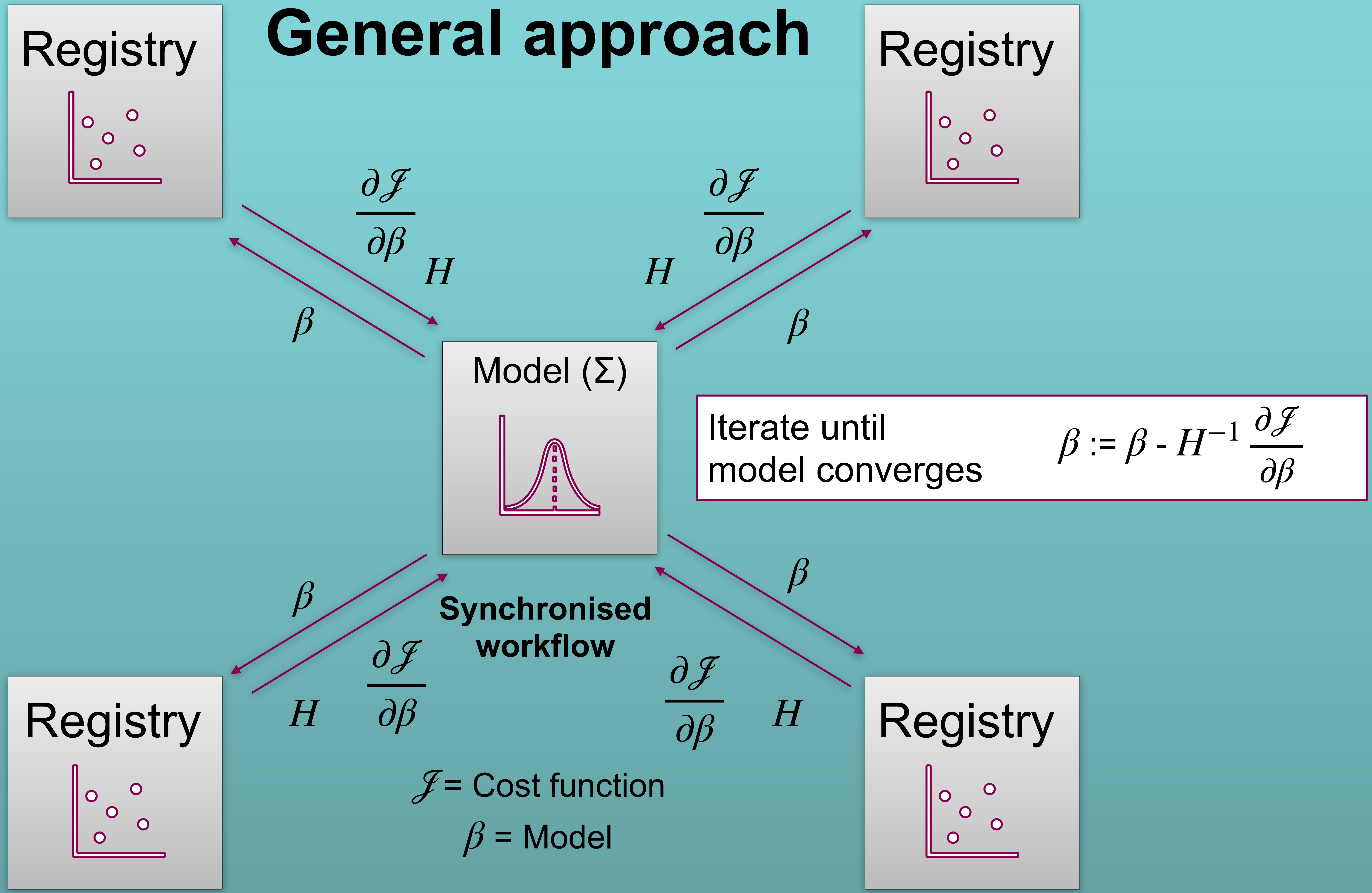
$$\beta := \beta - \alpha \frac{\partial \mathcal{J}}{\partial \beta}$$ Gradient descent

$$\beta := \beta - H^{-1} \frac{\partial \mathcal{J}}{\partial \beta}$$ Newton Raphson

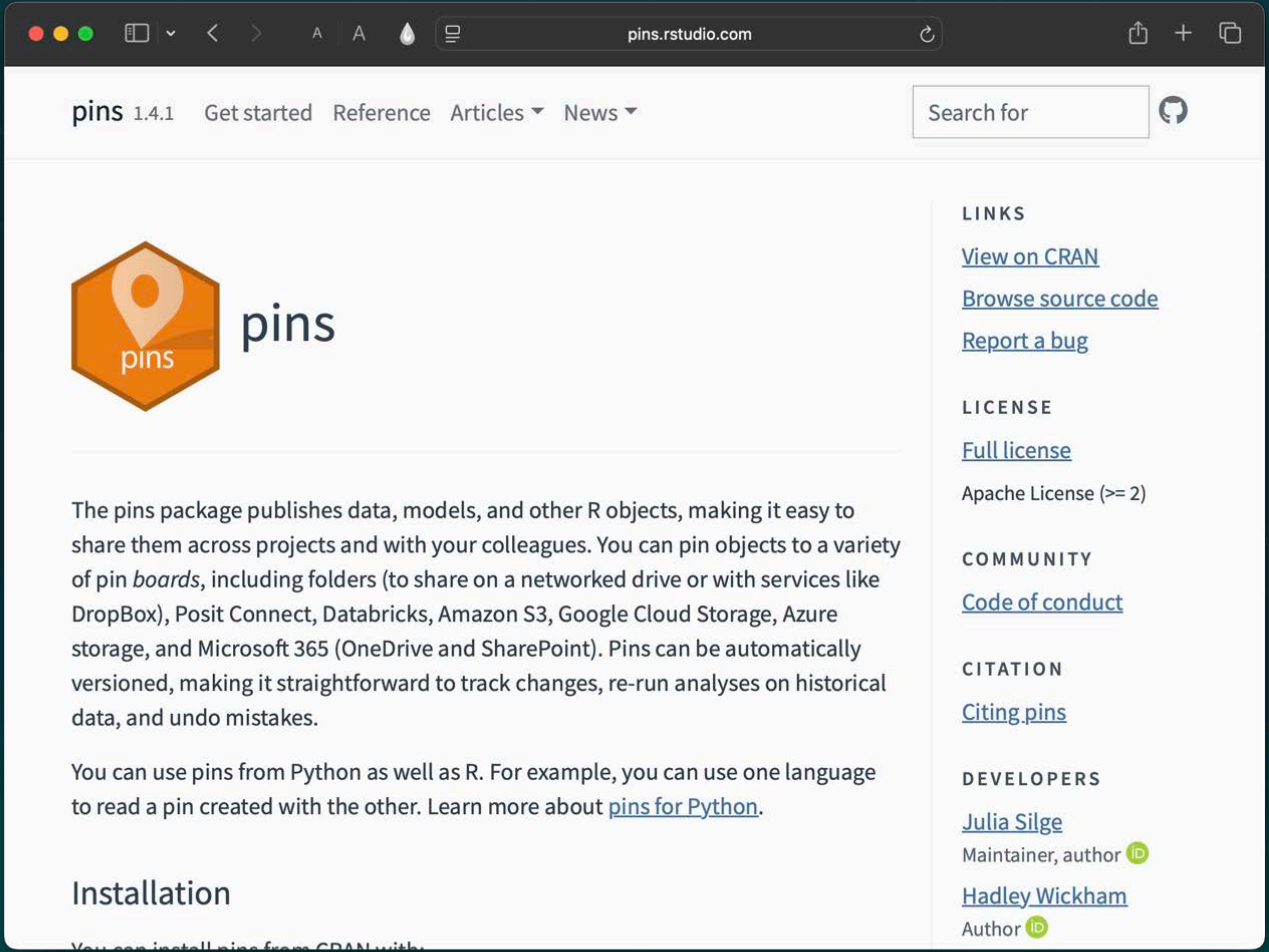
Hessian

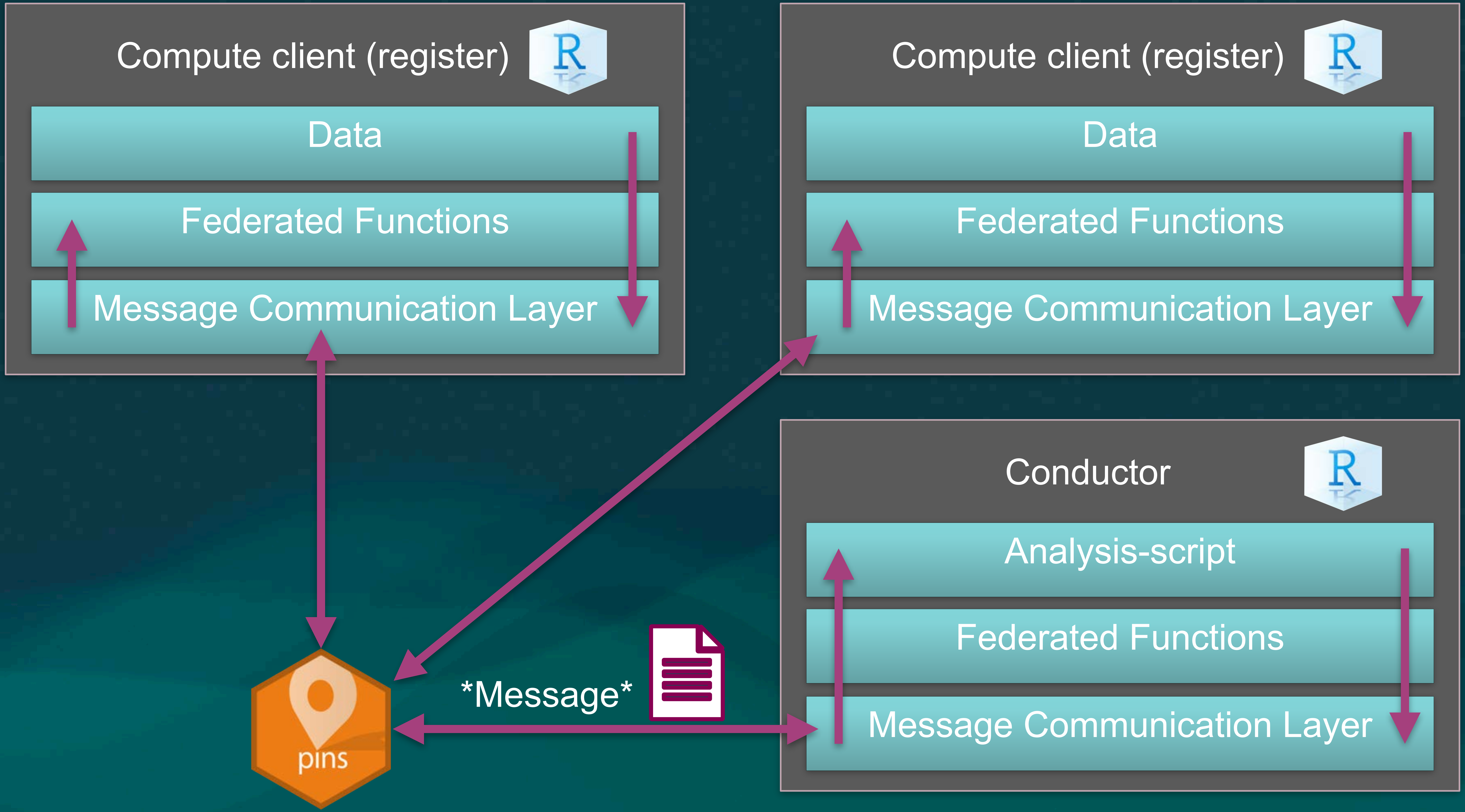
$$H(f) = \begin{bmatrix} \frac{\partial^2 f}{\partial x_1^2} & \frac{\partial^2 f}{\partial x_1 \partial x_2} & \cdots & \frac{\partial^2 f}{\partial x_1 \partial x_n} \\ \frac{\partial^2 f}{\partial x_2 \partial x_1} & \frac{\partial^2 f}{\partial x_2^2} & \cdots & \frac{\partial^2 f}{\partial x_2 \partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial^2 f}{\partial x_n \partial x_1} & \frac{\partial^2 f}{\partial x_n \partial x_2} & \cdots & \frac{\partial^2 f}{\partial x_n^2} \end{bmatrix}$$

Federated learning
General approach



- Dropbox
- S3
- Google Drive
- OneDrive




Compute client (register)
Data
Federated Functions
Message Communication Layer
Compute client (register)
Data
Federated Functions
Message Communication Layer
Conductor
Analysis-script
Federated Functions
Message Communication Layer
Message
pins

Case study. Logistic regression for PS weights across four registries (Italy, Czech Republic, Denmark, Sweden)

BIG MS

- Emulate clinical trial of relapses between RTX+OCR vs DMF
- Transform data to CDM
- Inclusion criteria: age 18-60, EDSS ≤ 5.5, RTX/OCR or DMF treatment
- Study period:
  - 2018 - 2021
- Part 1. Run logistic regression to obtain PS weights for two study arms:
  - P(AntiCD20) ~ age + sex + timetoindex + pastrelapse + pastrelapse*registry + registry
- Part 2. Run log binomial with weights to compare AntiCD-20 treatment vs DMF relapse outcome during two year follow-up (to be analysed):
  - P(relapse) ~ AntiCD20

Cost function results across iterations: Running time 3 minutes

$$\mathcal{J}(\hat{y}, y) = \mathcal{J}(\sigma(\beta^T X), y) = \sum_i^n -(y_i \log(\hat{y}_i) + (1 - y_i) \log(1 - \hat{y}_i))$$

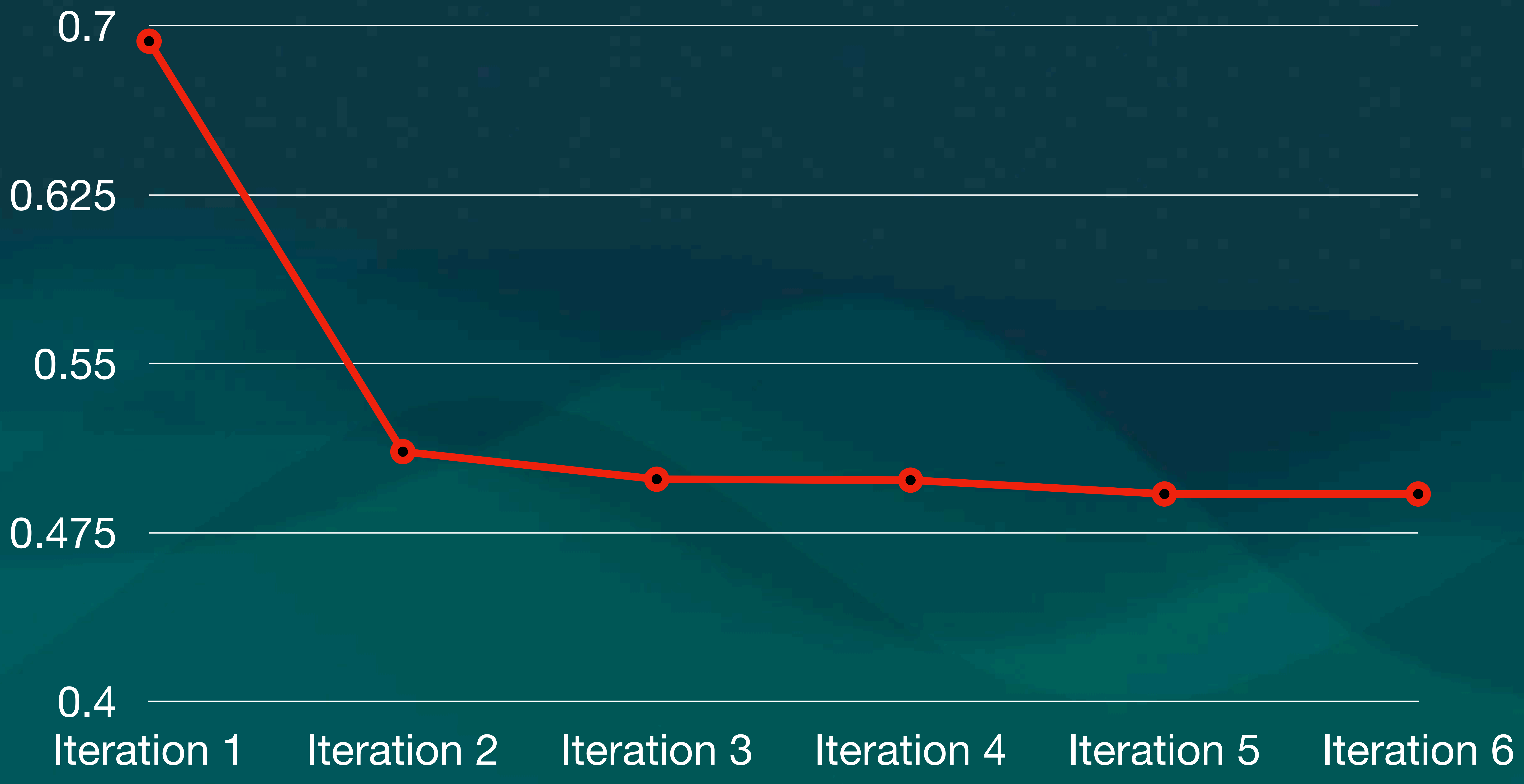


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Table 5: Average values before applying weights. Inclusion year 2018.

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RTX+OCR time to index	5.80	6.12	6.21	6.03	5.99	time = 1.88%
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Table 6: Average values after applying weights. Inclusion year 2018.

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RTX+OCR time to index	5.76	6.06	6.16	5.93	5.94	time = 0.51%
DMF time to index	5.94	6.33	5.62	5.86	5.95	(time diff = 0.01)
RTX+OCR Relapse %	22.68	47.27	78.13	46.76	67.88	relapse = 0.44%
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All done with federated learning

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Thank You

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DMF Women %	70.27	71.85	77.81	69.38	70.72	(sex diff = 5.80)
RTX+OCR time to index	5.80	6.12	6.21	6.03	5.99	time = 1.88%
DMF time to index	5.76	6.27	5.51	5.78	5.86	(time diff = 0.13)
RTX+OCR Relapse %	22.74	57.62	76.55	42.19	64.92	relapse = 5.05%
DMF Relapse %	22.40	38.82	81.14	49.63	70.72	(relapse diff = 5.80)

Table 6: Average values after applying weights. Inclusion year 2018.

	SMSR	DMSR	ReMuS	IMSR	Total	SMD
N RTX+OCR	2721.61	1365.43	944.72	2722.27	7001.94	86.1%
N DMF	668.39	1623.12	679.12	4901.69	6282.08	75.9%
RTX+OCR mean age	40.36	40.88	40.21	41.21	40.86	age = 1.04%
DMF mean age	41.64	43.10	40.07	39.82	40.91	(age diff = 0.05)
RTX+OCR Women %	68.36	66.66	68.52	68.06	67.88	sex = 0.89%
DMF Women %	65.48	67.85	74.53	66.98	67.57	(sex diff = 0.31)
RTX+OCR time to index	5.76	6.06	6.16	5.93	5.94	time = 0.51%
DMF time to index	5.94	6.33	5.62	5.86	5.95	(time diff = 0.01)
RTX+OCR Relapse %	22.68	47.27	78.13	46.76	67.88	relapse = 0.44%
DMF Relapse %	23.06	48.11	78.01	46.90	67.57	(relapse diff = 0.31)