Using mathematics to understand why insulin resistance is bad for you, but can be good for your cells

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Type 2 diabetes

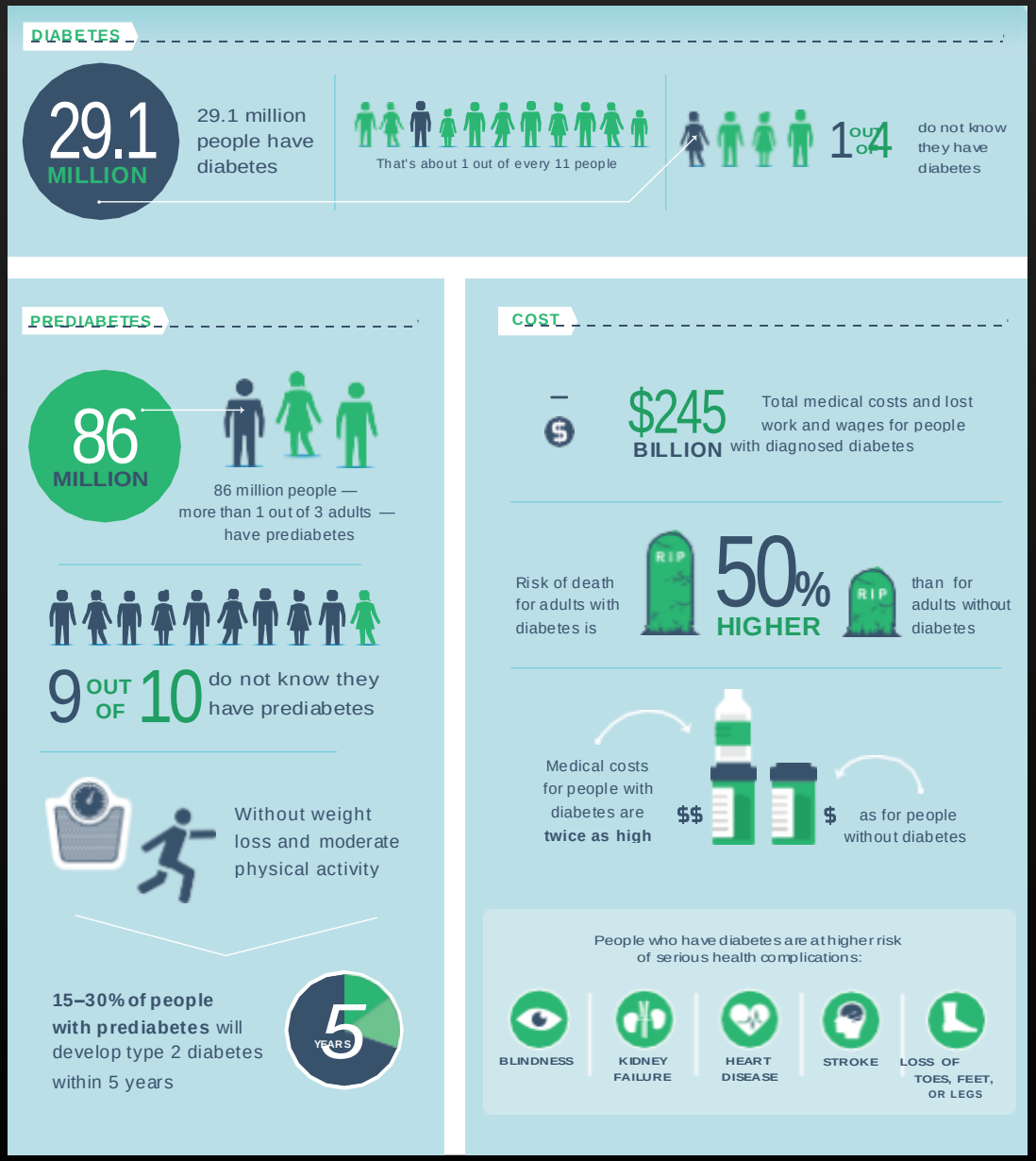


Figure: http://www.cdc.gov//diabetes/pubs/statsreport14/diabetes-infographic.pdf

What *is* type 2 diabetes?

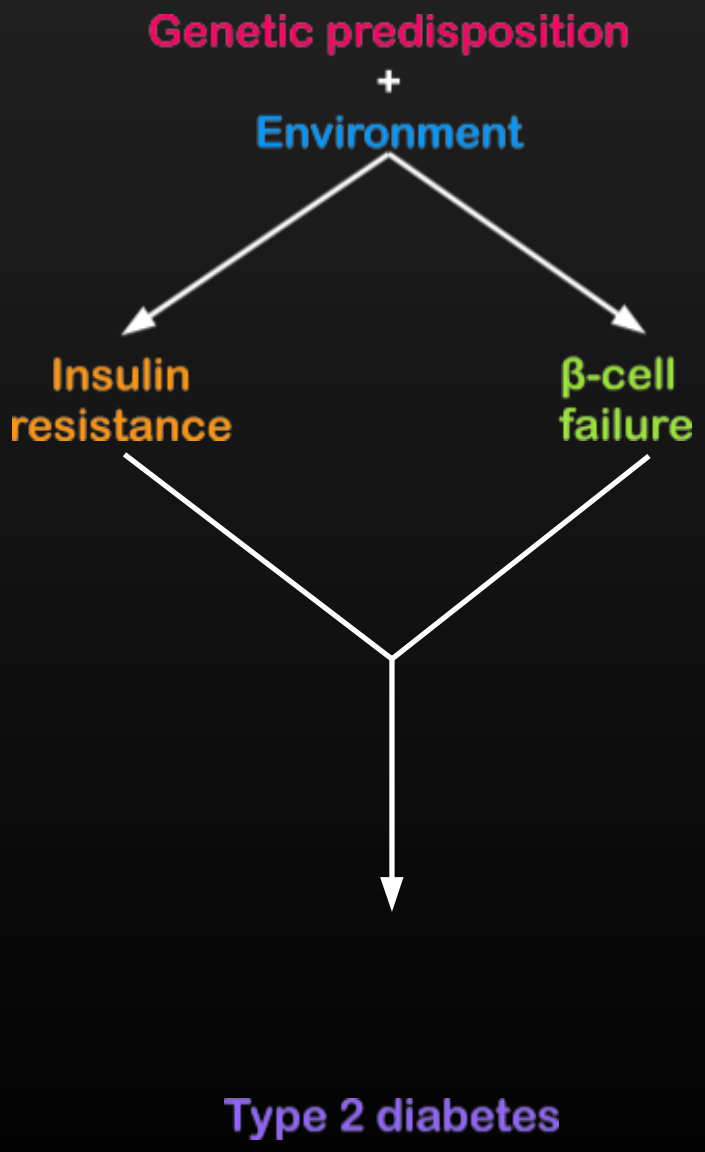
Two major players:

- glucose main energy source for most cells
- insulin produced by pancreatic *β* cells;
  signals cells to take up glucose from blood

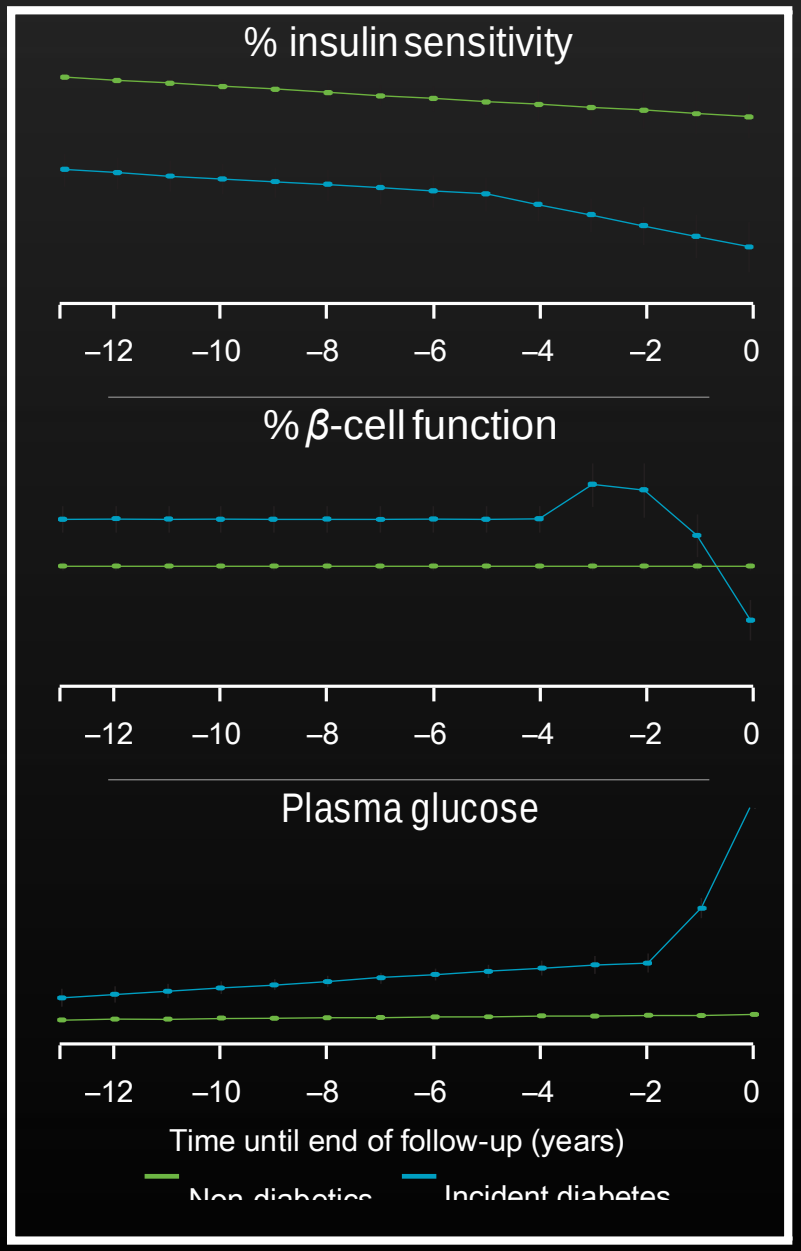
The disease:

- defined by severe hyperglycemia
- caused by combination of
  - insulin resistance
  - *β*-cell failure
- influenced by genetics and environment
-

  characterized by insufficient insulin



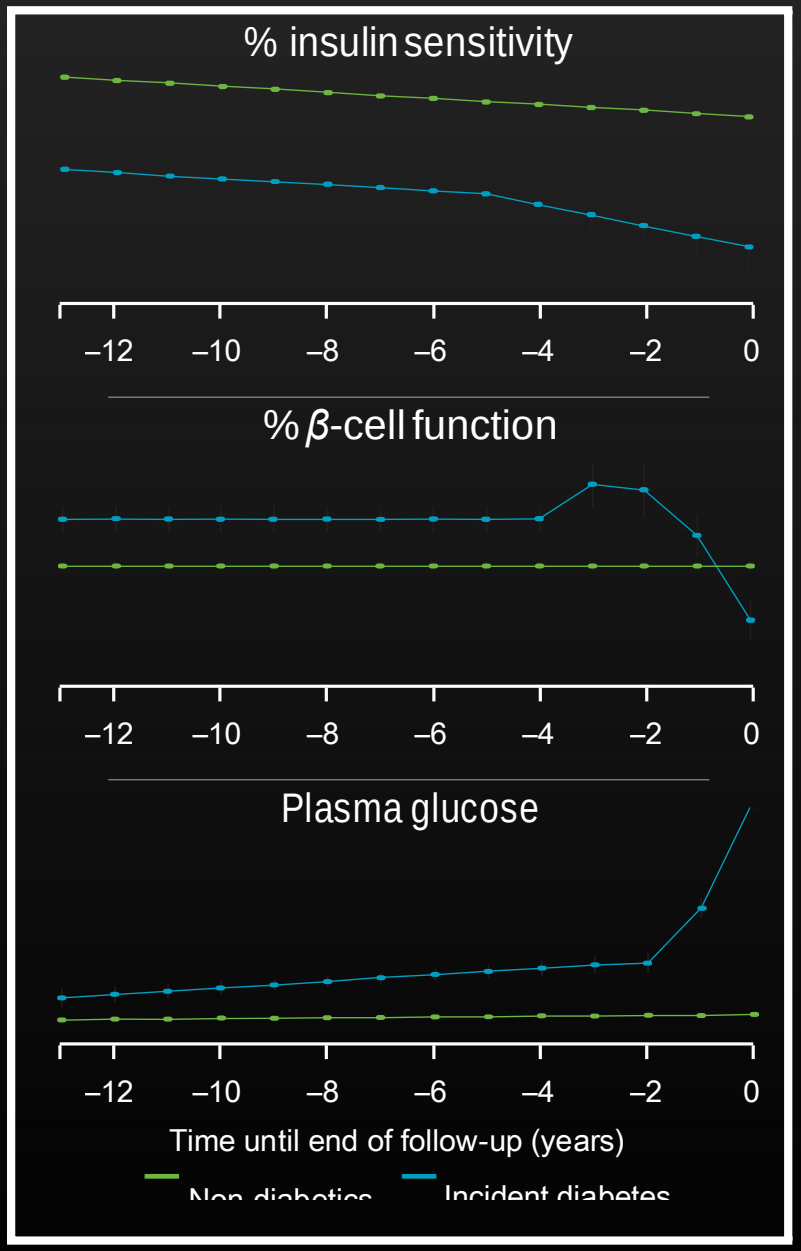
Type 2 diabetes dynamics



- decline in insulin sensitivity* with time
- severe insulin resistance in diabetics
- β-cell compensation for insulin resistance
- β-cell failure initiates diabetic hyperglycemia

* insulin sensitivity $\dfrac{1}{\text{insulin resistance}}$

Type 2 diabetes dynamics



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* insulin sensitivity $\propto \frac{1}{\text{insulin resistance}}$

The problem: precise mechanisms of the development of insulin resistance and β-cell dysfunction are unclear.

Where we begin

PNAS

Insulin resistance is a cellular antioxidant defense mechanism

Kyle L. Hoehn[a,1,2,3], Adam B. Salmon[b,1], Cordula Hohnen-Behrens[a], Nigel Turner[a], Andrew J. Hoy[a], Ghassan J. Maghzal[c], Roland Stocker[c], Holly Van Remmen[b], Edward W. Kraegen[a], Greg J. Cooney[a], Arlan R. Richardson[b], and David E. James[a,2]

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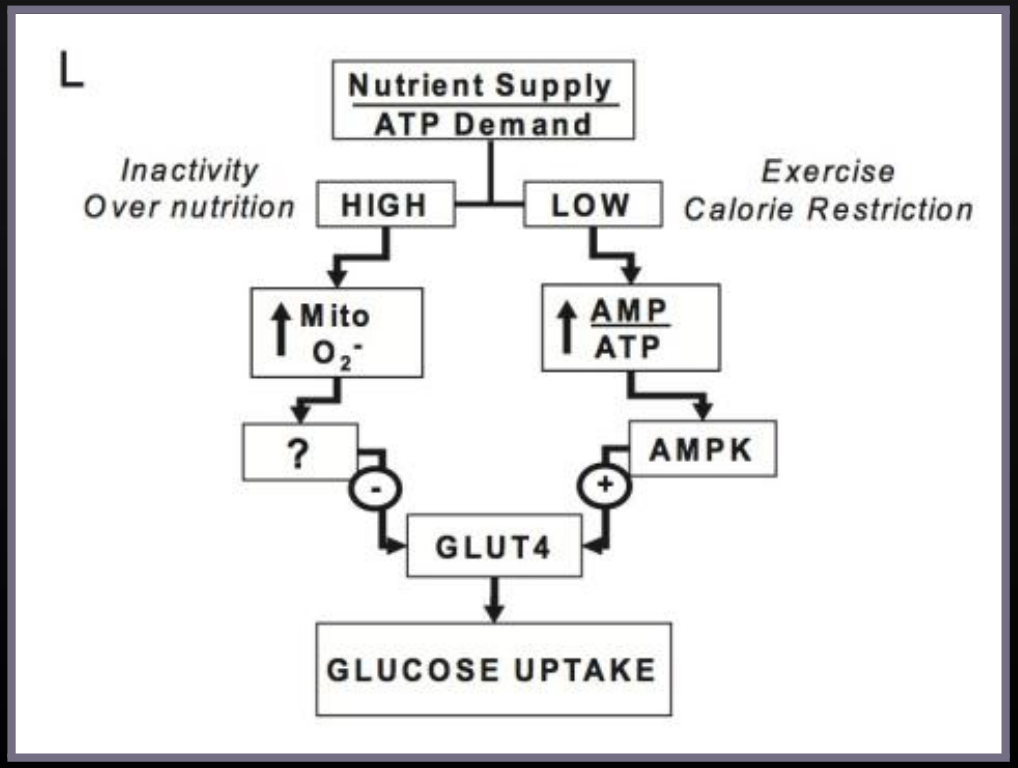
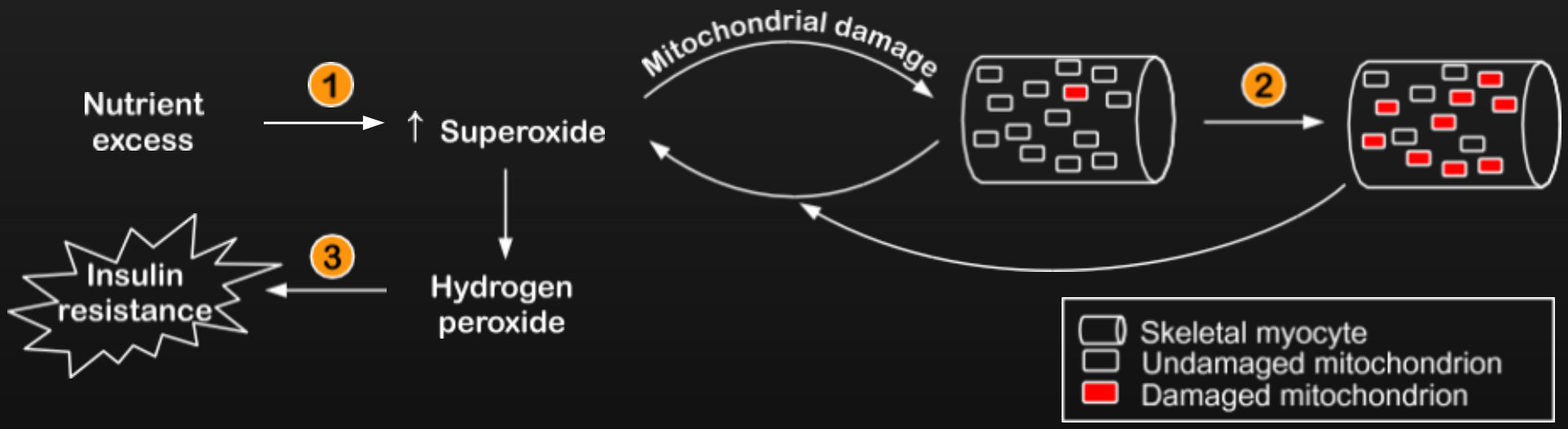


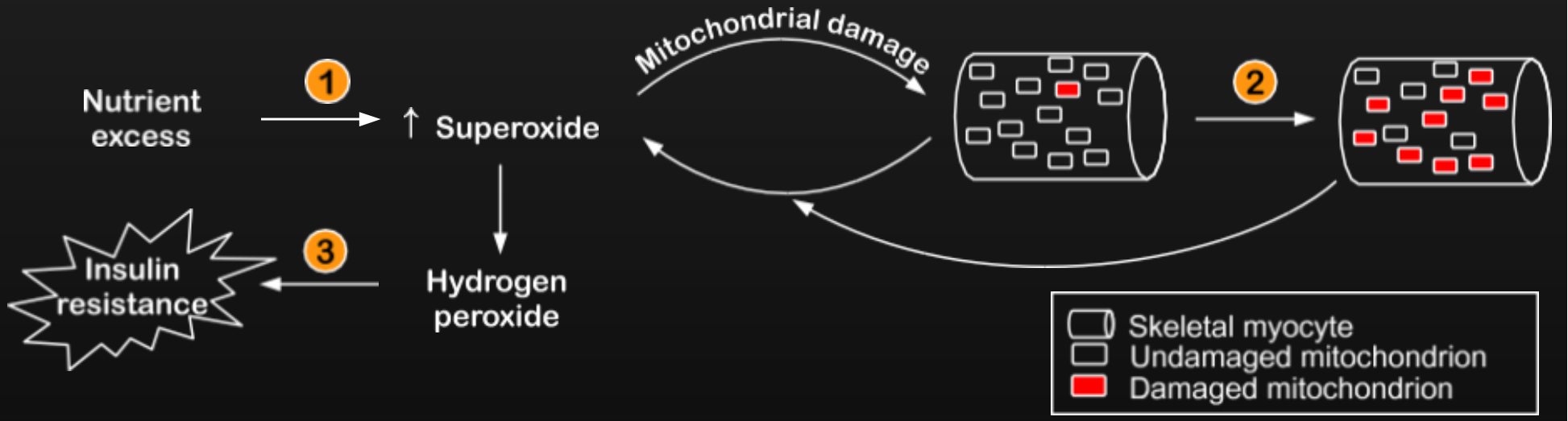
Skeletal muscle insulin resistance



Oxidative stress accumulation of reactive oxygen species,

e.g., superoxide, hydrogen peroxide

Skeletal muscle insulin resistance

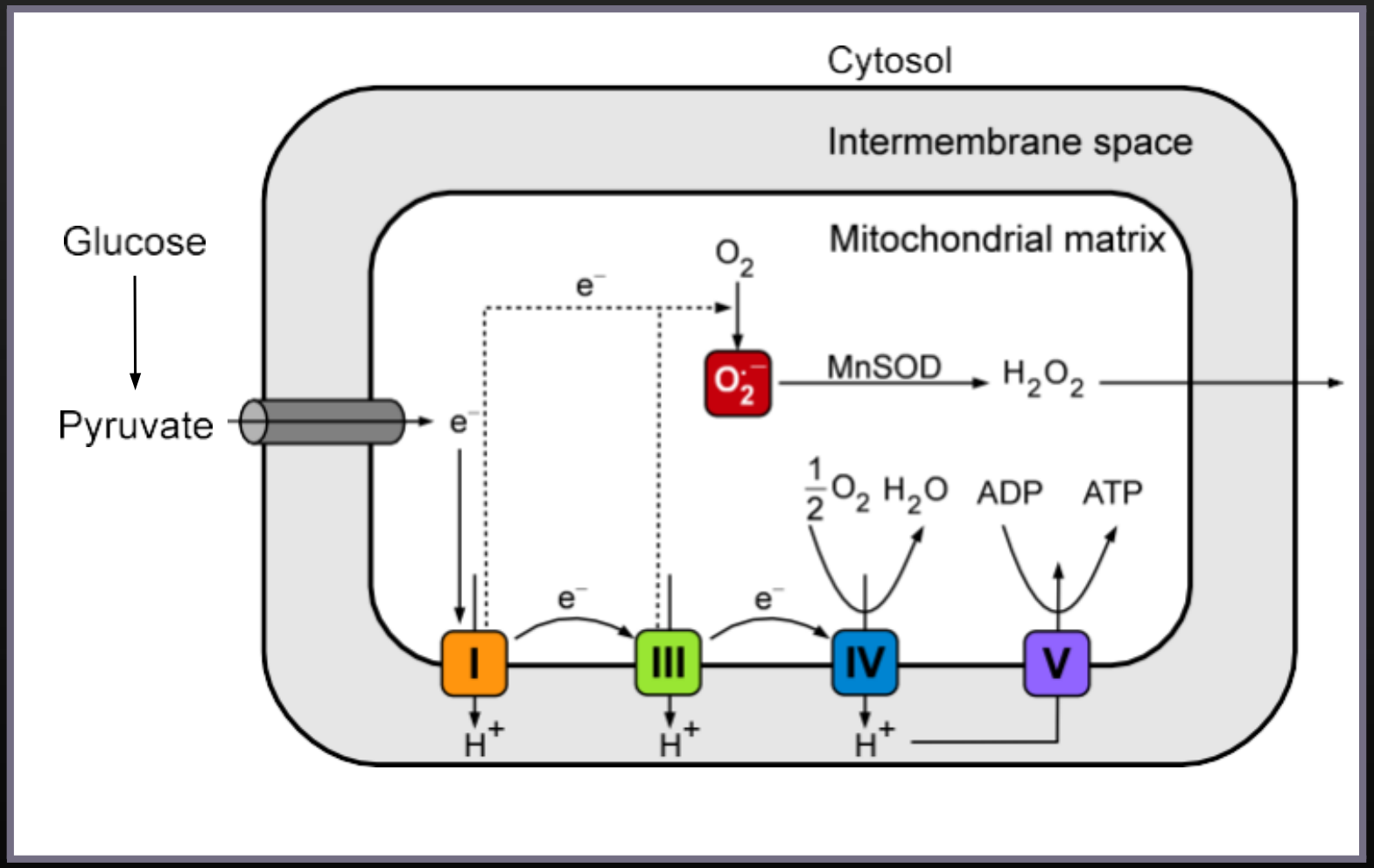


1 superoxide production

2

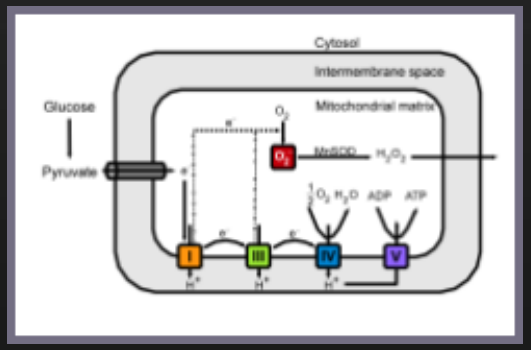
3

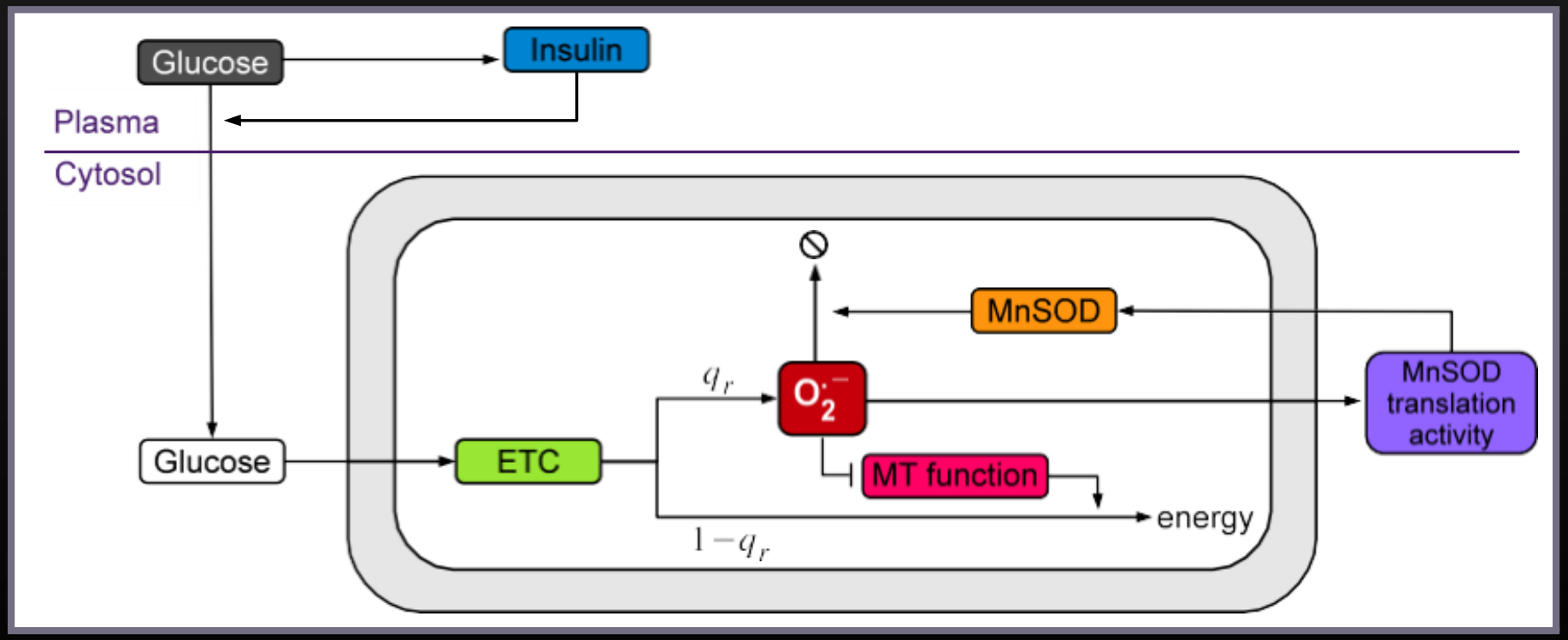
Subsystem I: superoxide production



- e-: electron
- H^+: proton
- $O_2^{\cdot-}$: superoxide
- MnSOD: antioxidant, manganese superoxide dismutase
- H_2O_2: hydrogen peroxide

Subsystem I: superoxide production





- ETC: electron transport chain
- MT: mitochondrial

Subsystem I equations

? ΔG reference parameter for food intake, with σ an increasing function of ΔG.

? ***F*** mitochondrial function variable; form specified in feedback coupling.

Plasma glucose:

$$\frac{dG}{dt} = \underbrace{\sigma}_{\text{food intake}} + \underbrace{h_g}_{\text{production}} - \underbrace{k_g G}_{\text{insulin-independent uptake}} - \underbrace{SGI}_{\text{insulin-dependent uptake}}$$

Plasma insulin:

$$\frac{dI}{dt} = \underbrace{h_i B \frac{G^2}{G^2 + G_h^2}}_{\text{production}} - \underbrace{k_i I}_{\text{clearance}}$$

Intracellular glucose:

$$\frac{dG_i}{dt} = \underbrace{\gamma_1 SGI}_{\text{uptake from plasma}} - \underbrace{k_{gi} G_i}_{\text{glucose processing}}$$

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ETC activity:

$$\frac{dC}{dt} = \underbrace{v_2 k_{gi} G_i (C_{tot} - C)}_{\text{activation}} - \underbrace{k_c C}_{\text{energy production}} \left[(1 - q_r)F + \underbrace{q_r}_{\text{superoxide production}} \right]$$

Superoxide:

$$\frac{dR_S}{dt} = \underbrace{k_{cr} q_r C}_{\text{production}} - \underbrace{k_{rs} R_S A_S}_{\text{removal}} - \underbrace{\delta_R R_S^3}_{\text{inactivation}}$$

Antioxidant:

$$\frac{dA_S}{dt} = \underbrace{q_a E}_{\text{production}} - \underbrace{q_a k_{rs} R_S A_S}_{\text{superoxide toxicity}}$$

Antioxidant production:

$$\frac{dE}{dt} = \underbrace{d_e R_S (1 - E)}_{\text{activation}} - \underbrace{k_e E^2}_{\text{deactivation}}$$

Mitochondrial dysfunction: assumptions

1 Homogeneity:

⟶altered respiratory activity

- damaged mitochondrial lipids/proteins

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Feedback model I: Mitochondrial Inefficiency Model (MIM)

$$\frac{dL}{dt} \quad \xi(1-L)\frac{X^2}{X^2+\lambda^2}, \text{ where } X \quad \frac{R_s/(R_s+A_s)}{R_{s0}/(R_{s0}+A_{s0})} - 1.$$

$$\Rightarrow F_{MIM} = 1 - L$$

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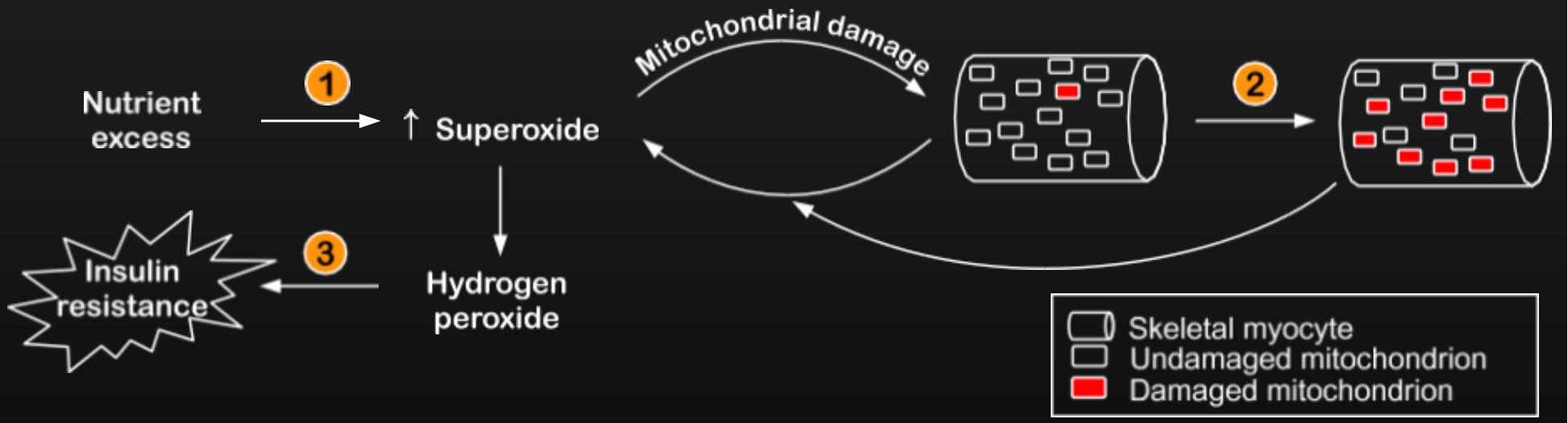
2 Heterogeneity:

⟶abnormal population dynamics

- 'sufficient' mutant mtDNA clonal expansion
- mitochondrial swelling and membrane permeability
- stress from accumulation of damaged content

Skeletal muscle insulin resistance



1

2 mitochondrial selection

3

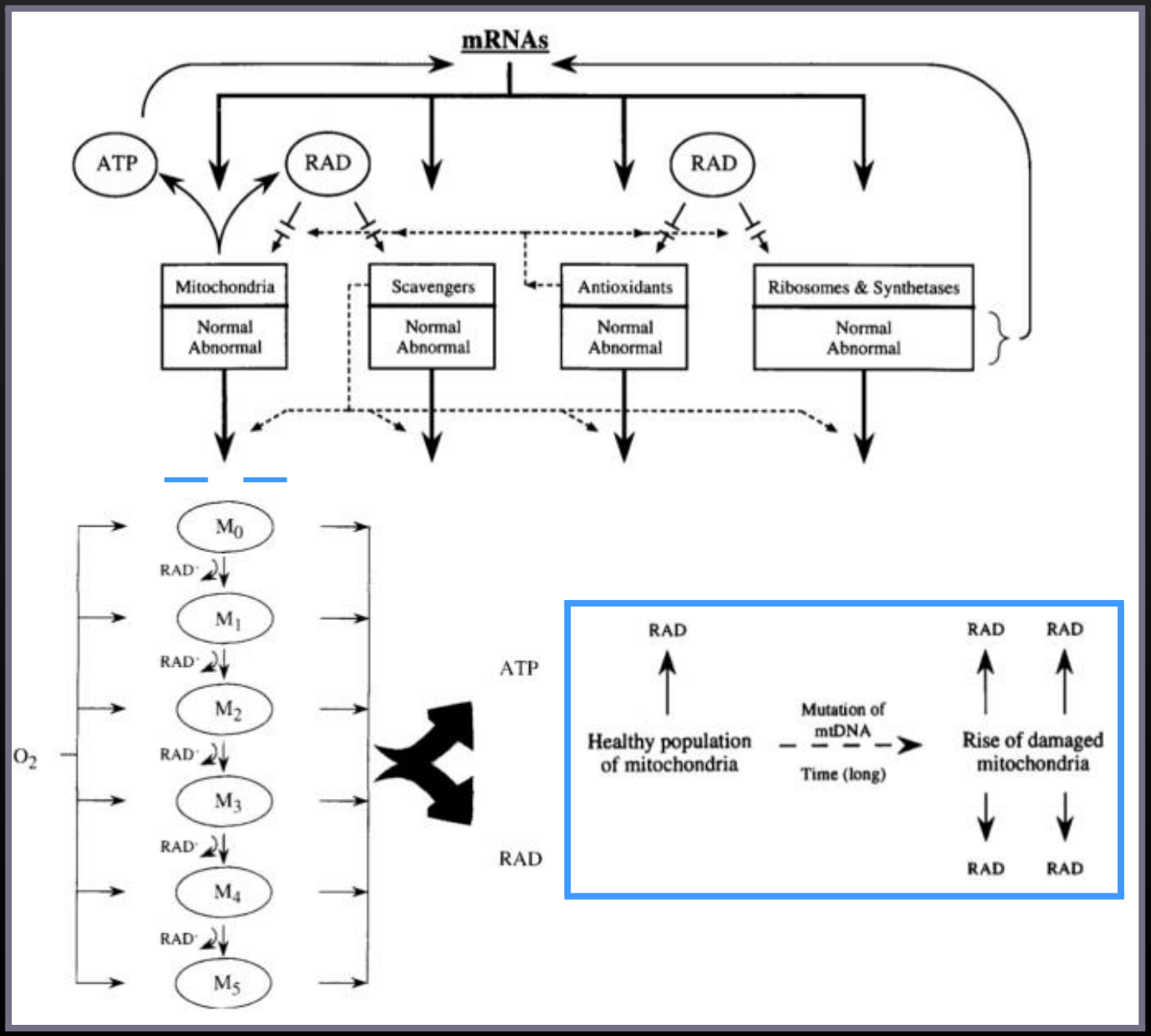
MARS: A network theory of aging

Mitochondria

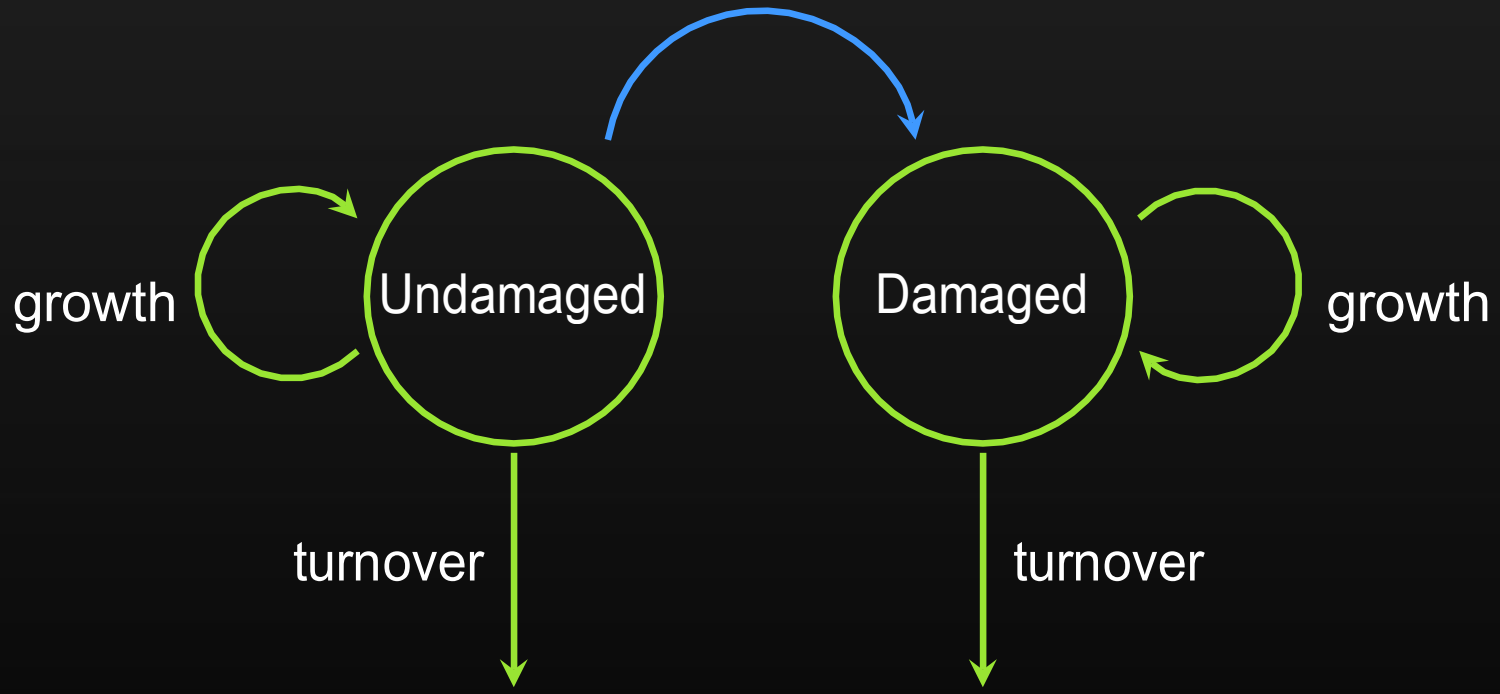
Aberrant proteins

Radicals

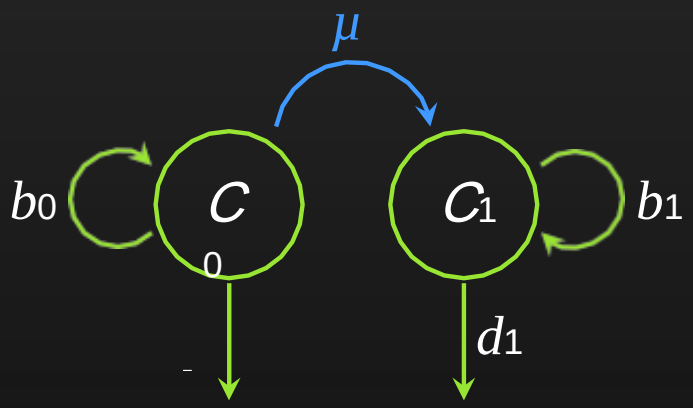
Scavengers



Subsystem II: mitochondrial selection



Modeling mitochondrial selection: setup



Two-state stochastic model

$M_0(t)$:= the number of healthy (class C_0) mitochondria at time t

$M_1(t)$:= the number of damaged (class C_1) mitochondria at time

t $M_0(t)$ + $M_1(t)$ K for all t; K is constant

Parameters

- selection parameters (s_r := fractional replicative difference; s_m := fractional turnover difference) $\in (-1, 1)$
- b_1 $(1 + s_r)b_0$
- d_1 $(1 + s_m)d_0$

“Null selection” $\Rightarrow$

$s_m = s_r = 0$

Modeling mitochondrial selection: state transitions

Assume that each mitochondrial turnover event results in a growth event.

Transition matrix

$$A \quad \begin{array}{l} \\ \Delta M_0 \\ \Delta M_1 \end{array} \begin{array}{ccc} \# & \# & \# \\ 1 & -1 & 0 \\ -1 & 1 & 0 \end{array} \quad [A_1\, A_2\, A_3]$$

Transition probabilities

$$p_i \quad \Pr(A_1 / M_0 \quad i) \quad \frac{d_1(K-i)}{\underbrace{d_0 i + d_1 (K-i)}_{\text{death from } C_1}} \quad \frac{(1-\mu) b_0 i}{\underbrace{b_0 i + b_1 (K-i)}_{\text{birth to } C_0}}$$

$$q_i \quad \Pr(A_2 / M_0 \quad i) \quad \frac{d_0 i}{\underbrace{d_0 i + d_1 (K-i)}_{\text{death from } C_0}} \quad \frac{\mu b_0 i + b_1 (K-i)}{\underbrace{b_0 i + b_1 (K-i)}_{\text{transition/birth to } C_1}}$$

$$\Rightarrow \quad \Pr(A_3 / M_0 \quad i) \quad 1 - p_i - q_i$$

Mean time to total damage

Let T_i := the expected time to total damage starting from i healthy mitochondria.

Let E_i := the mean waiting time between events for M_0 i, i.e.

E_i $[d_0 i + d_1(K - i)]^{-1}$.

$$T_i \quad q_i(T_{i-1} + E_i) + (1 - p_i - q_i)(T_i + E_i) + p_i(T_{i+1} + E_i)$$

lose a healthy one | no change | gain a healthy one

$$\Rightarrow \quad -E_i \quad q_i T_{i-1} - (p_i + q_i) T_i + p_i T_{i+1}$$

Solution

$$T_i \quad T_0 + \sum_{j=0}^{i-1} \eta_{j+1} + \sum_{m=0}^{i-2} \sum_{n=m+1}^{i-1} \eta_{K-m} \rho_{K-n}$$

for i $1, \ldots, K-1$, with η_i $\frac{E_i}{q_i}$, ρ_i $\frac{p_i}{q_i}$, T_0 0 and T_K $\eta_K + T_{K-1}$.

With null selection and constant μ: $T_K \approx 400$ years.

Superoxide-to-damage feedback

- damage transition: $\mu(t) := \mu_0 \left[1 + \rho \left(\frac{R_s(t)}{R_{s0}} - 1\right)\right]$

- probability distribution: $\pi_j(t) := \Pr(M_1 \quad j)$
  Master equation:

$$\frac{d\pi_0}{dt} \quad -\hat{q}_0\pi_0 + \hat{p}_1\pi_1, \ldots,$$

$$\frac{d\pi_j}{dt} \quad \hat{q}_{j-1}\pi_{j-1} - (\hat{q}_j + \hat{p}_j)\pi_j + \hat{p}_{j+1}\pi_{j+1}, \ldots,$$

$$\frac{d\pi_K}{dt} \quad \hat{q}_{K-1}\pi_{K-1} - \hat{p}_K\pi_K$$

- damage likelihood: $D(t) = \Pr(M_1 \geq 1) = \frac{1}{K} \sum_{j=1}^{K} \pi_j(t) \quad j$

Feedback models I – IV: specifying F

Complex: $\frac{dG_i}{dt} = v_2 k_{gi} G_i (C_{tot} - C) - k_c C[(1 - q_r)\boldsymbol{F} + q_r]$

1

$$F_{\mathrm{MIM}} = 1 - L$$

2

$$F_{\mathrm{DMM}} = 1 - D$$

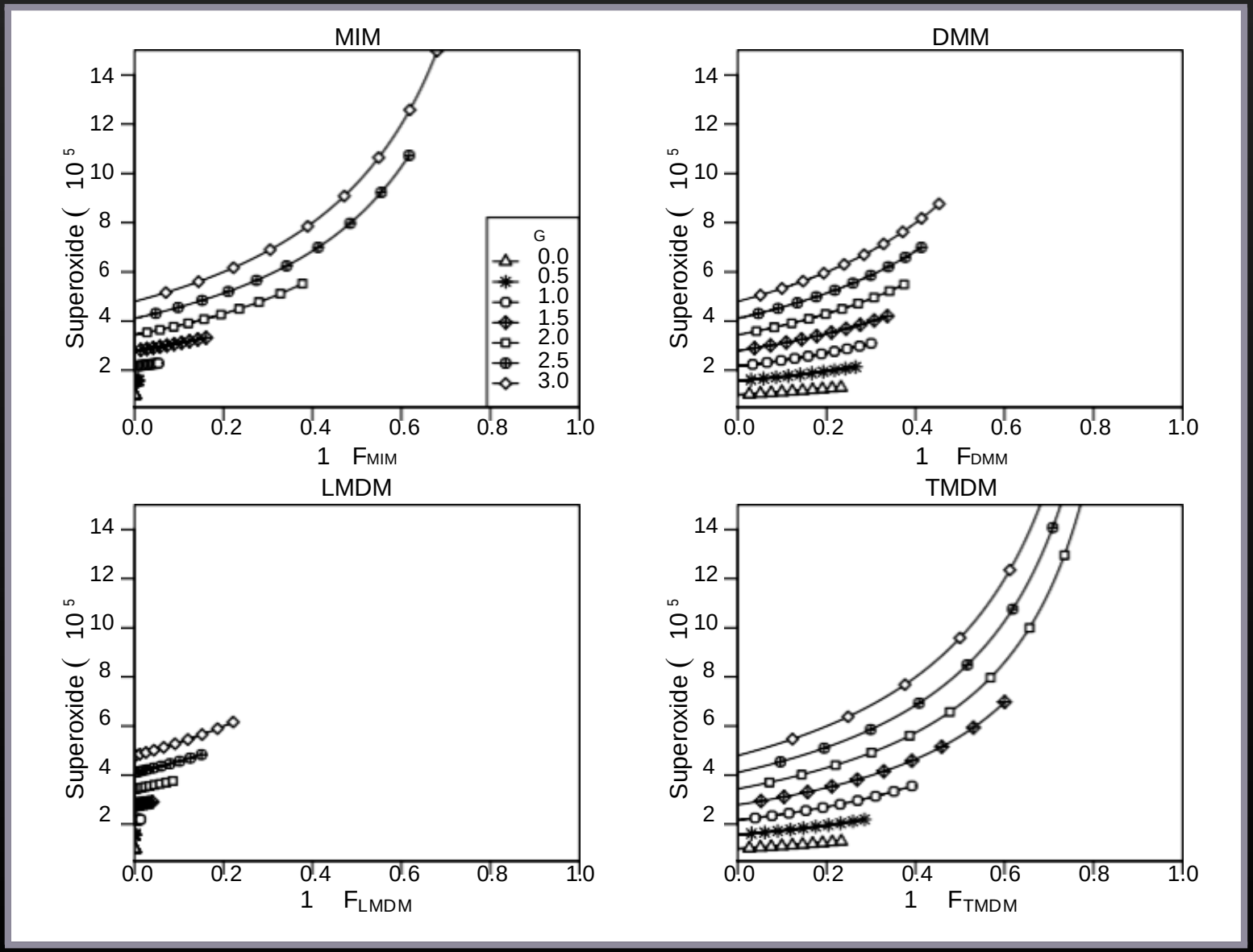
3

$$F_{\mathrm{LMDM}} = (1 - D) + D \cdot (1 - L)$$

4

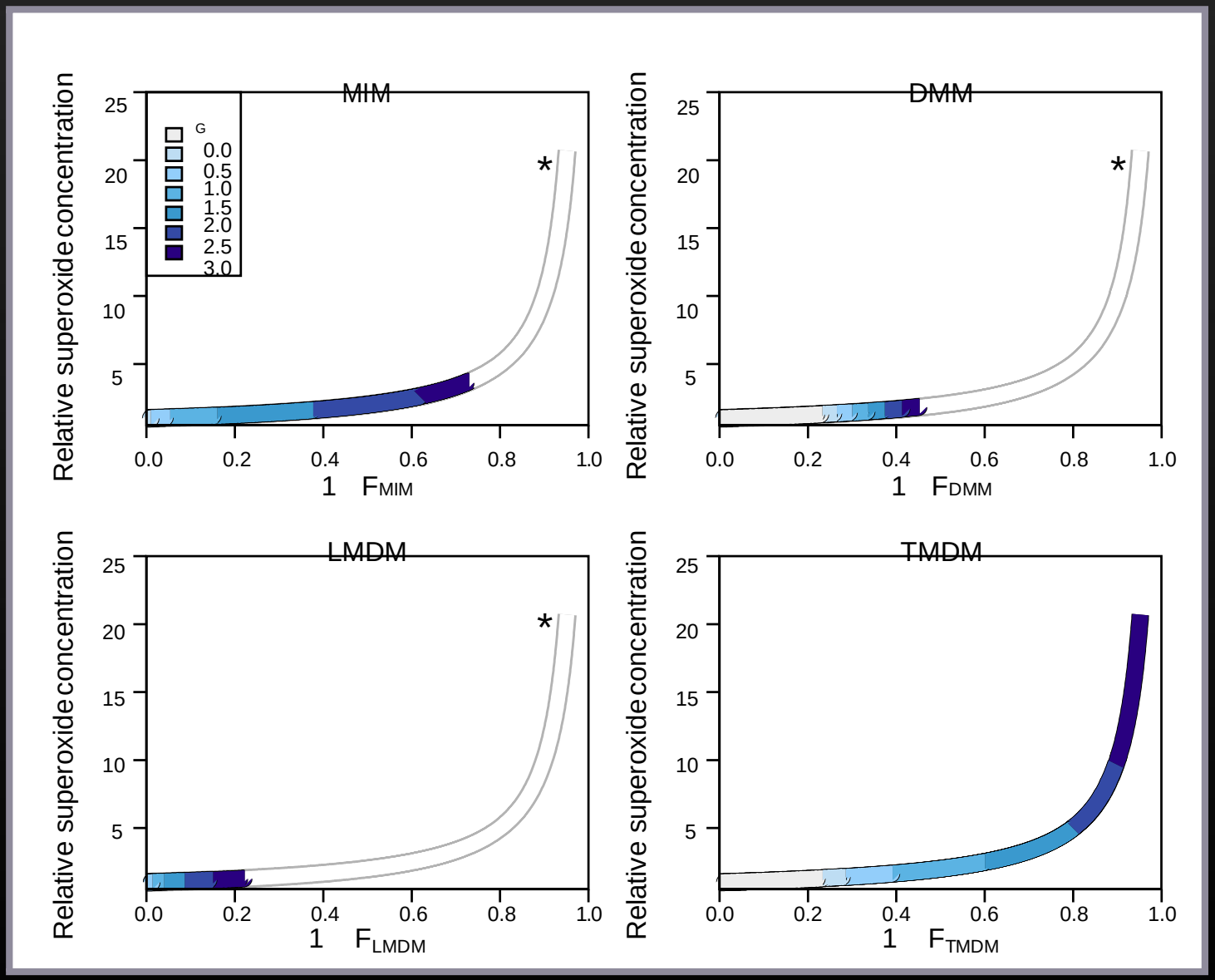
$$F_{\mathrm{TMDM}} = (1 - L)(1 - D)$$

Results I: null selection



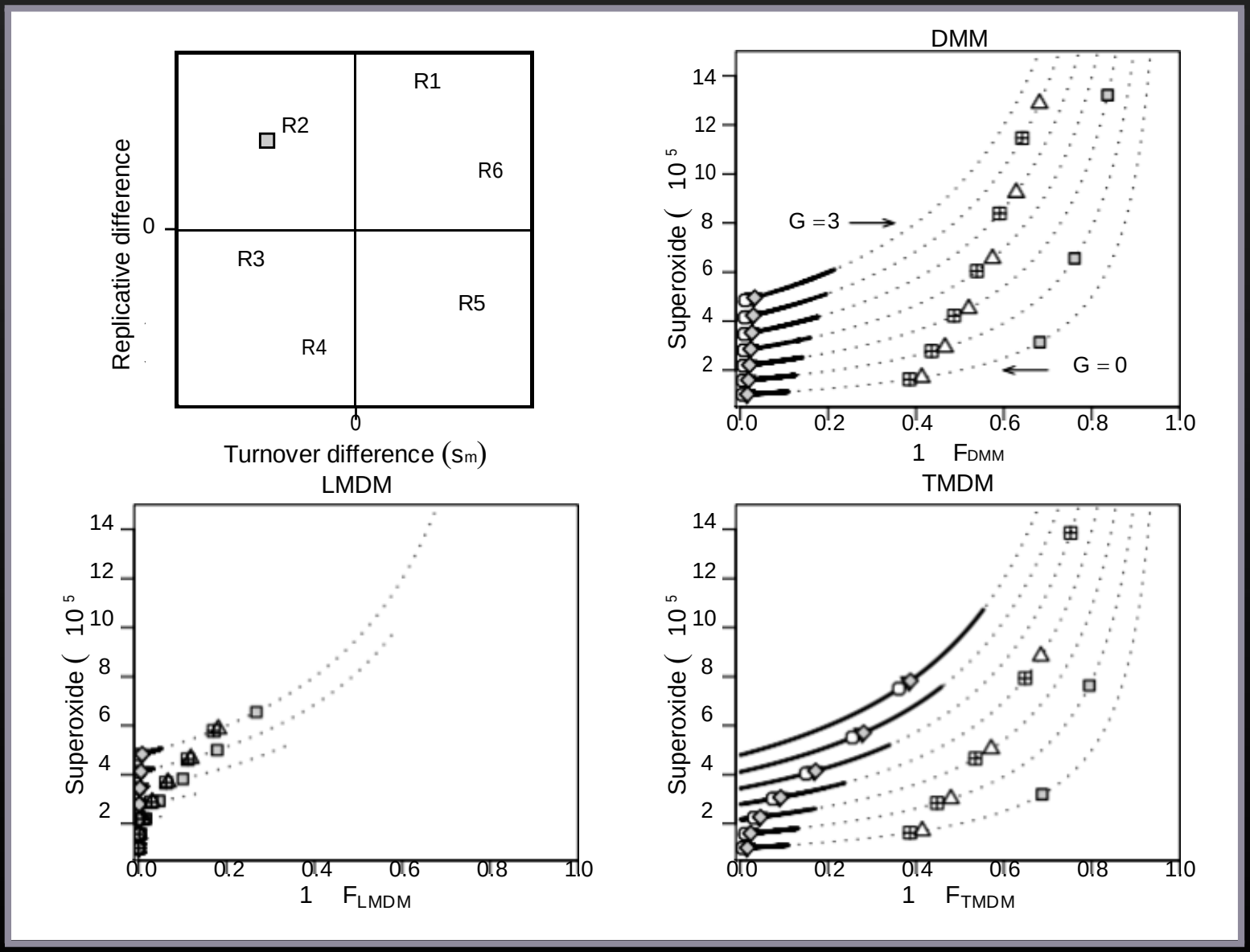
[ejg & Adler, 2014]

Results II: assessing the timing of dysfunction



[ejg & Adler, 2014]

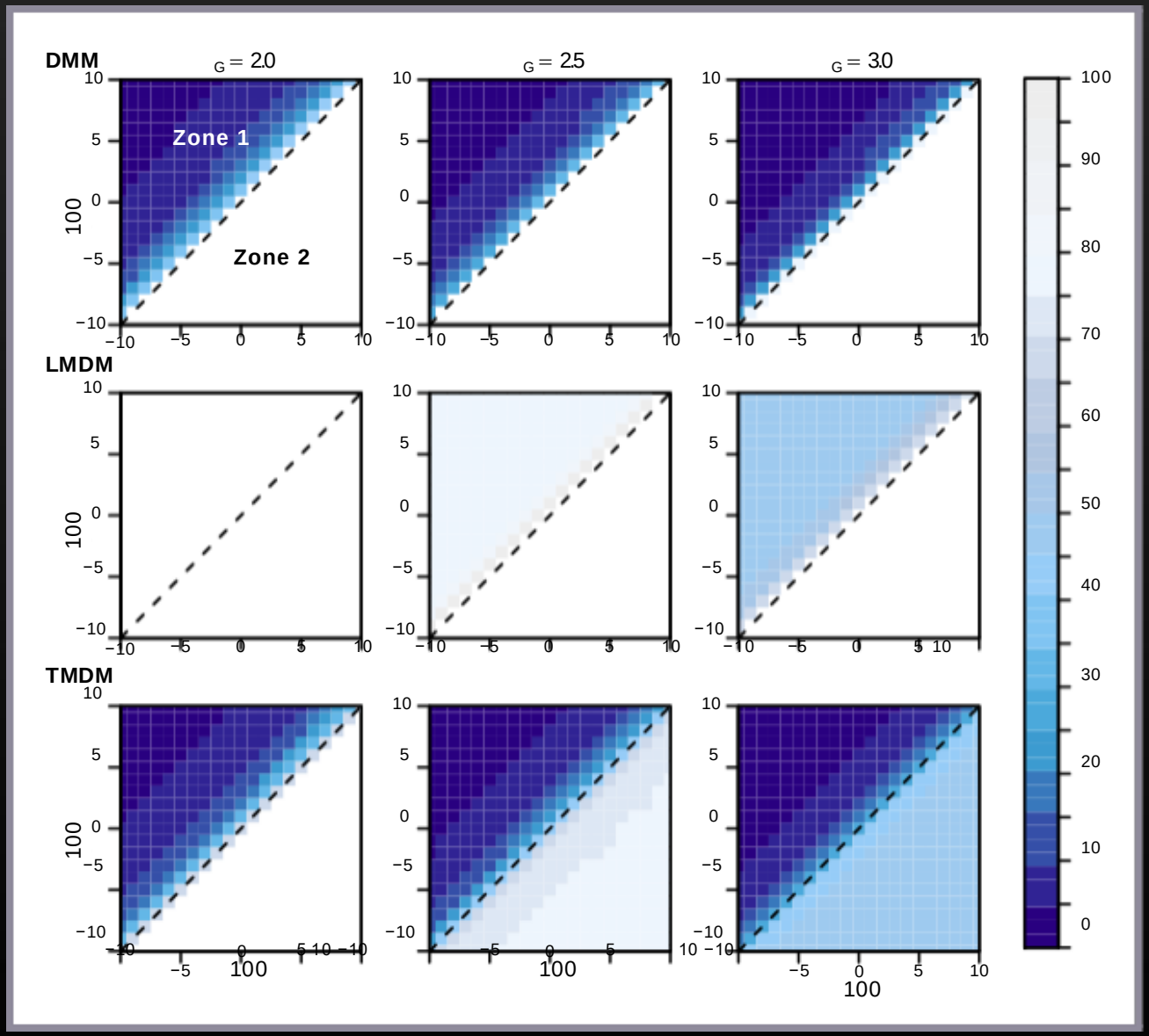
Results III: response to mitochondrial selection



Recall: $s_r = (b_1/b_0) - 1$; $s_m = (d_1/d_0) - 1$

[ejg & Adler, 2014]

Results IV: response to selection parameters



- compute age at which superoxide concentration exceeds threshold of 10^{-4} μM
- Zone 1: $s_r > s_m$
  Zone 2: $s_r < s_m$
- physiological restriction: $s_m > 0$

[ejg & Adler, 2014]

Why insulin resistance is bad for you, good for your cells

In susceptible individuals:

Intracellular response

↑ glucose uptake (good for you, bad for the cell)

↑ superoxide production

mitochondrial dysfunction

↑ oxidative stress

↓glucose uptake (bad for you); ↓superoxide production (good for the cell)

stress signal activation; impaired insulin signaling

Systemic response

↓ glucose uptake (bad for you)

↑ glucose uptake

Thank you!

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References

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