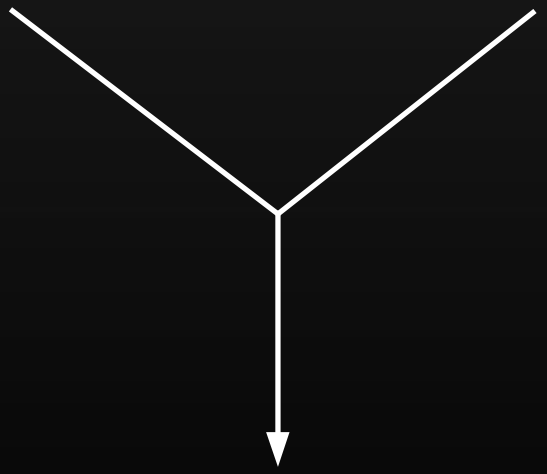
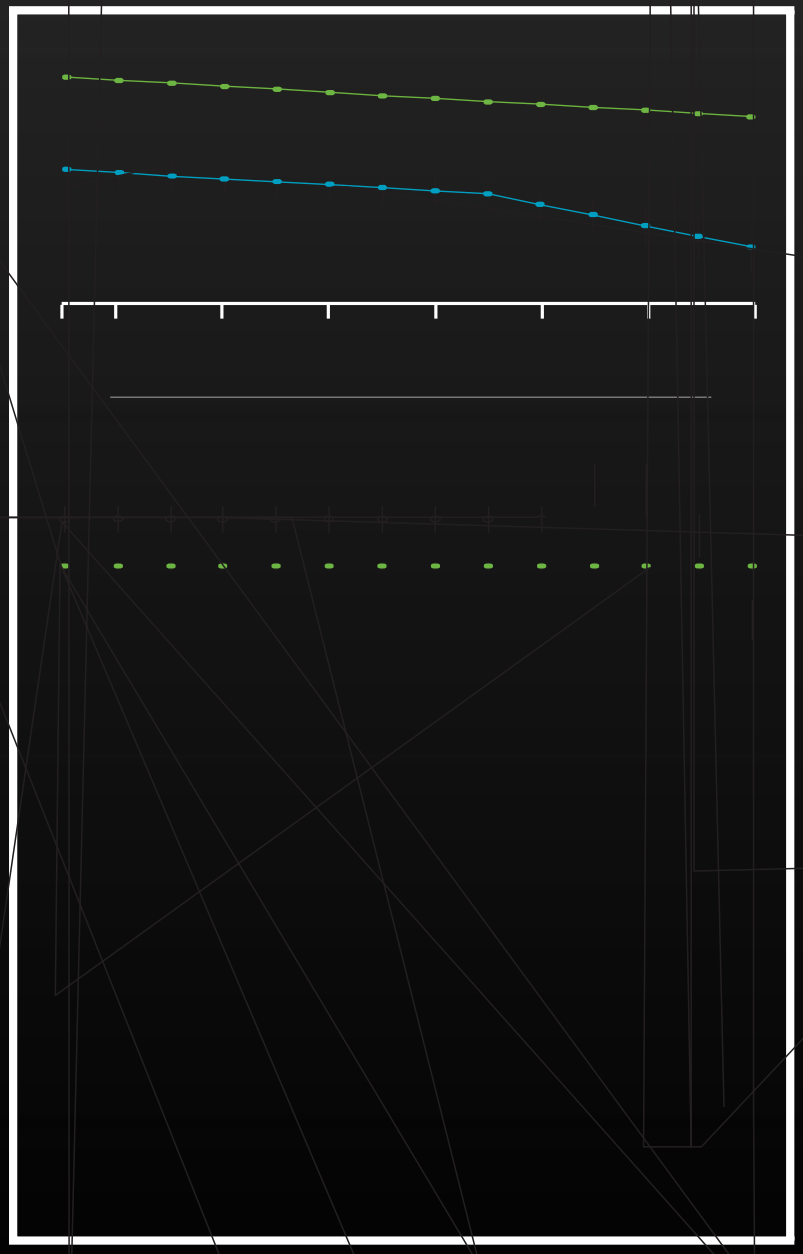
What *is* type 2 diabetes?

- insulin resistance
- -cell failure



Type 2 diabetes dynamics

Type 2 diabetes dynamics



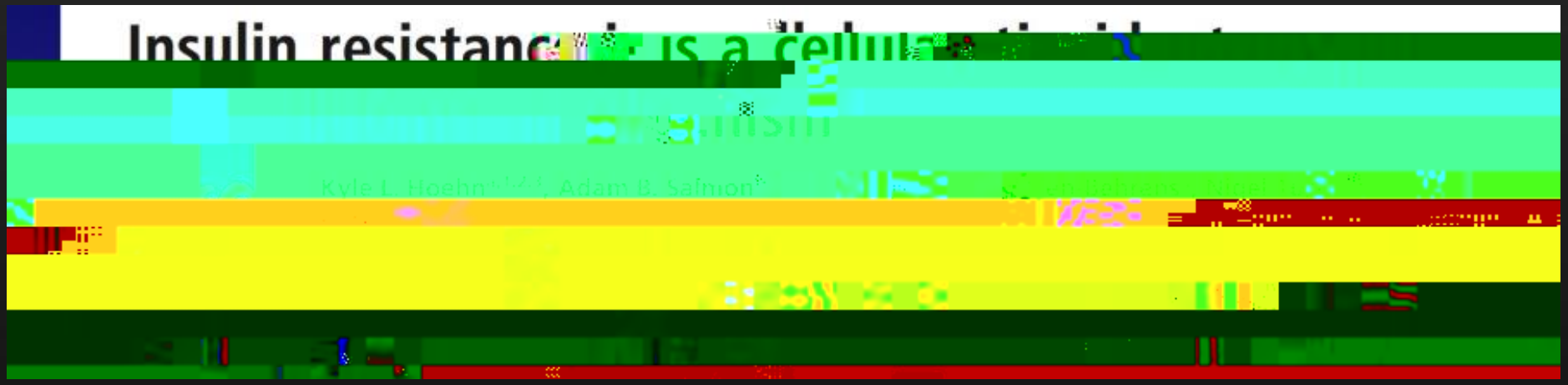
β

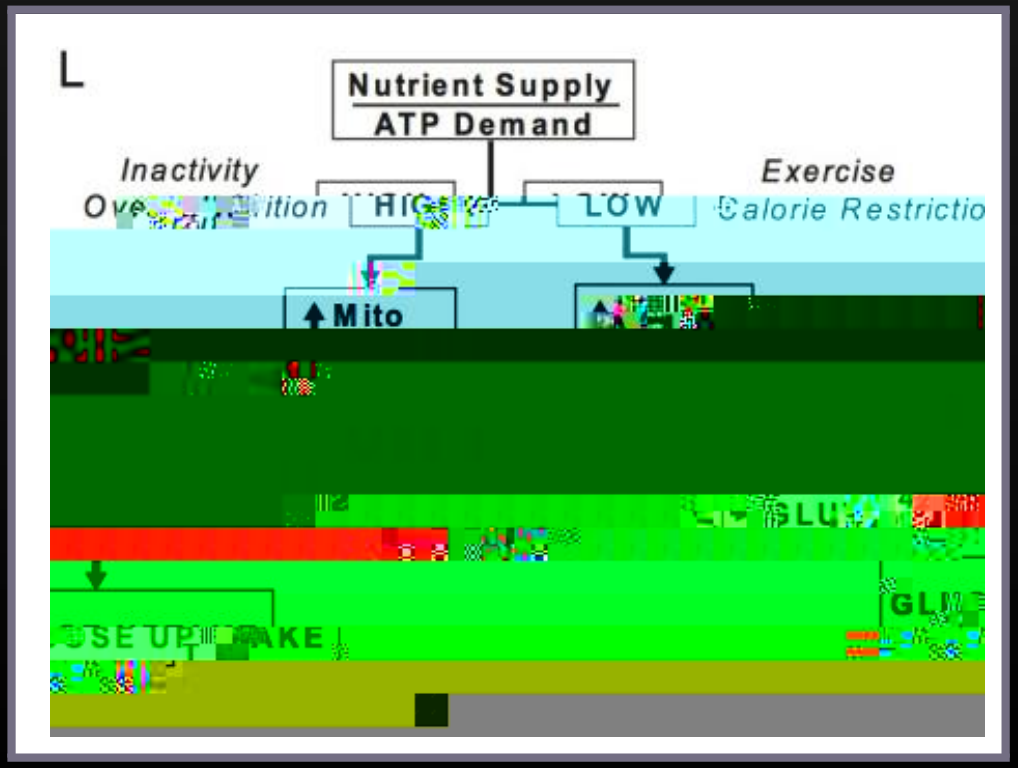
β

1

β

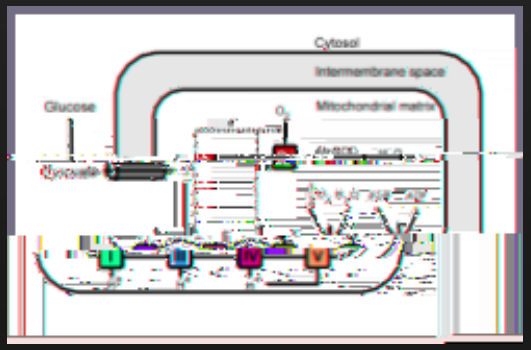
Where we begin

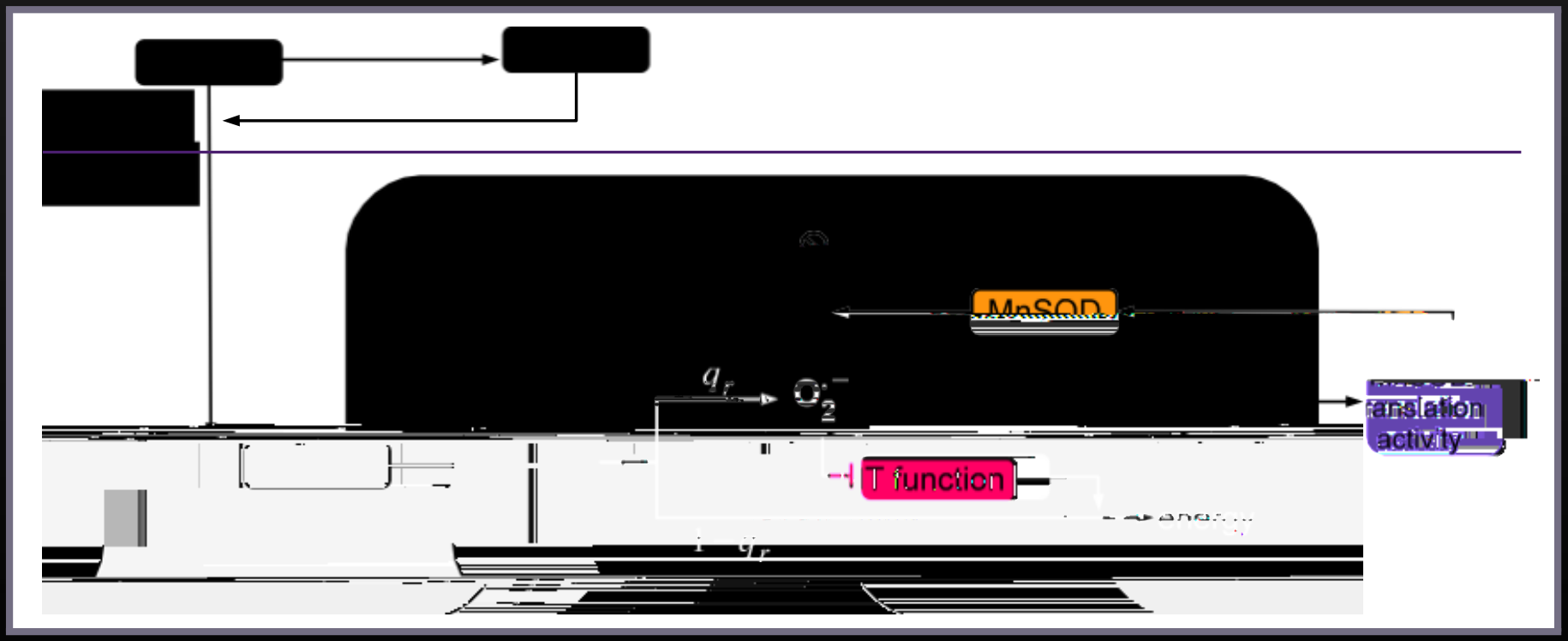




Skeletal muscle insulin resistance

Subsystem I: superoxide production





Subsystem I equations

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

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

Plasma glucose:

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

Plasma insulin:

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

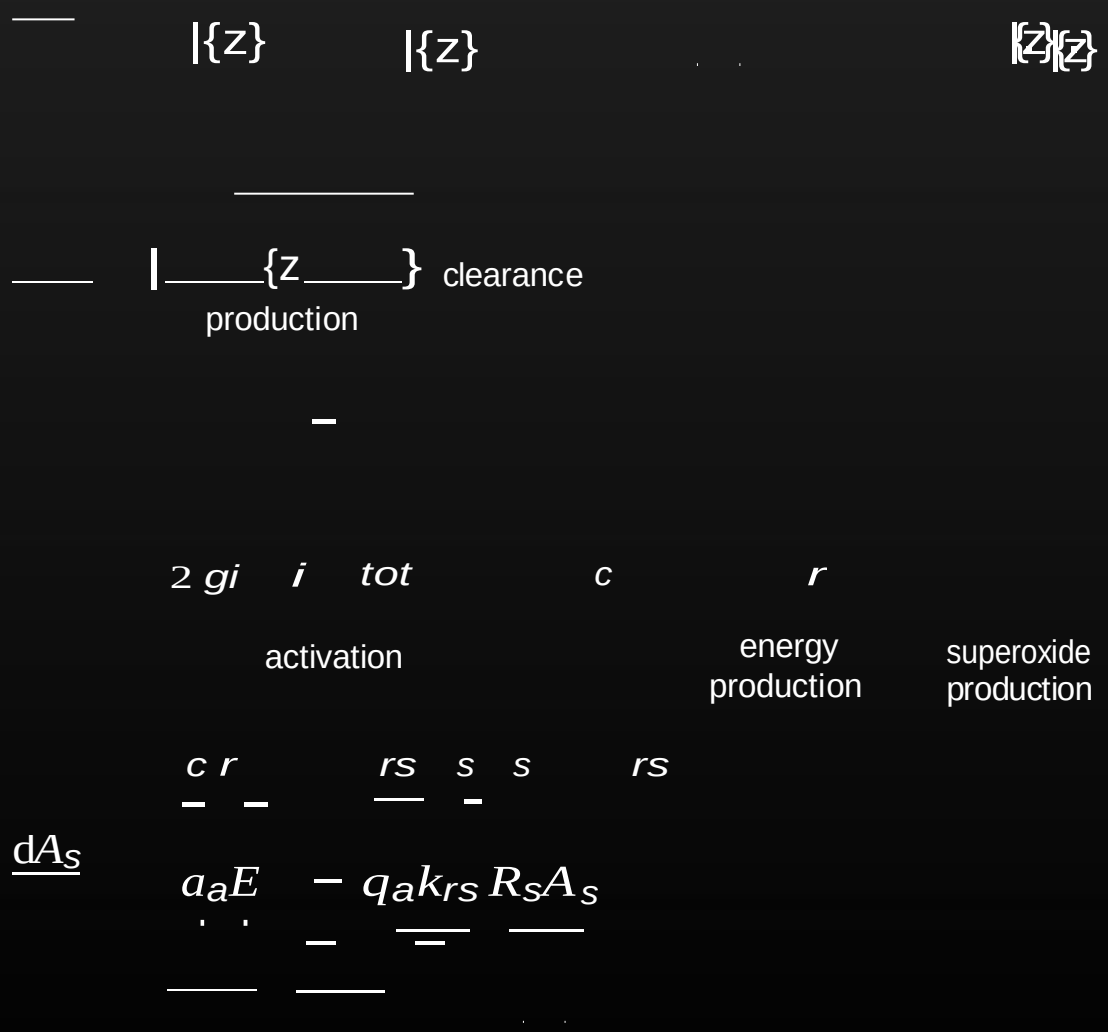
Intracellular glucose:

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

Subsystem I equations

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

?



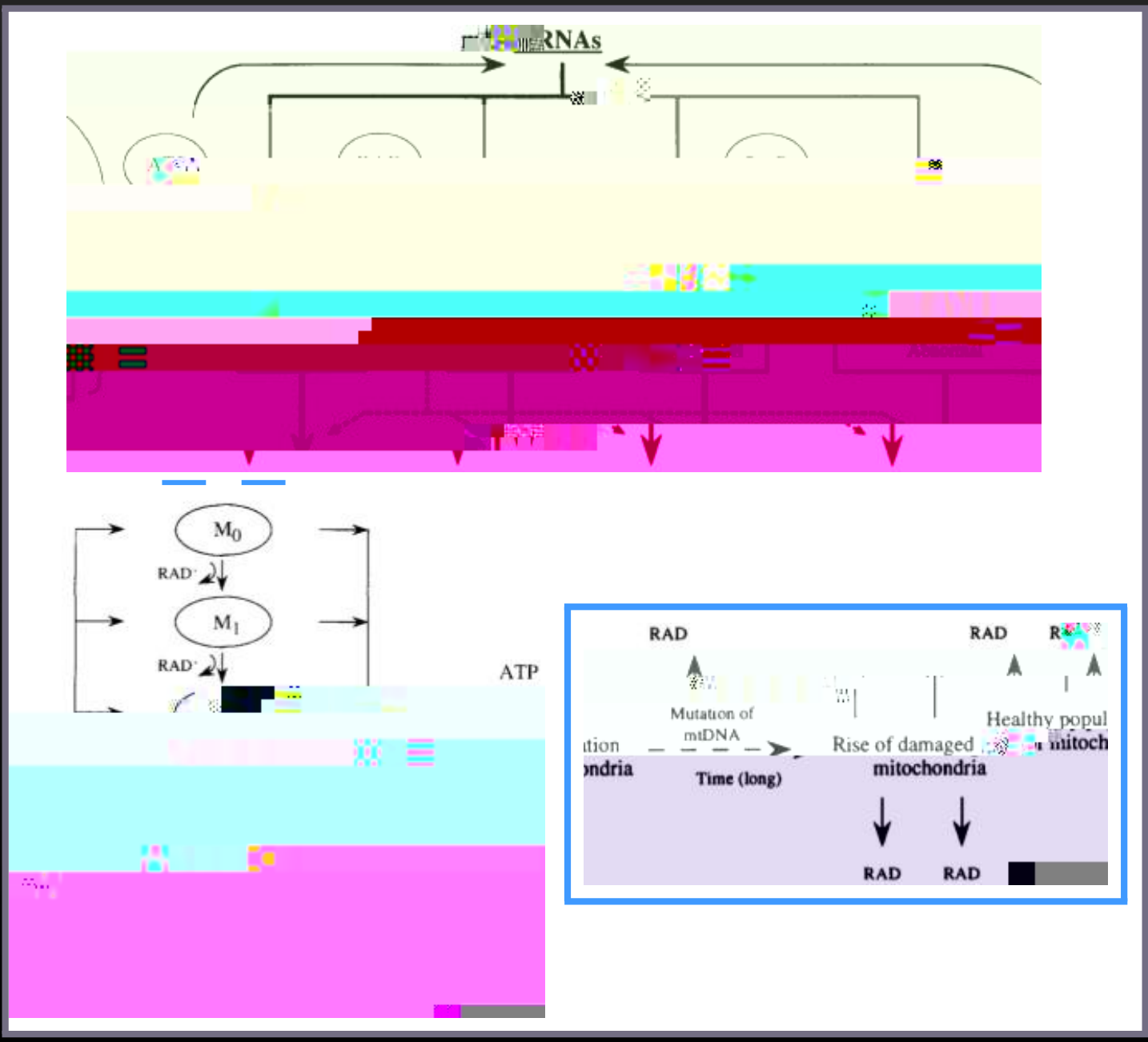
Mitochondrial dysfunction: assumptions

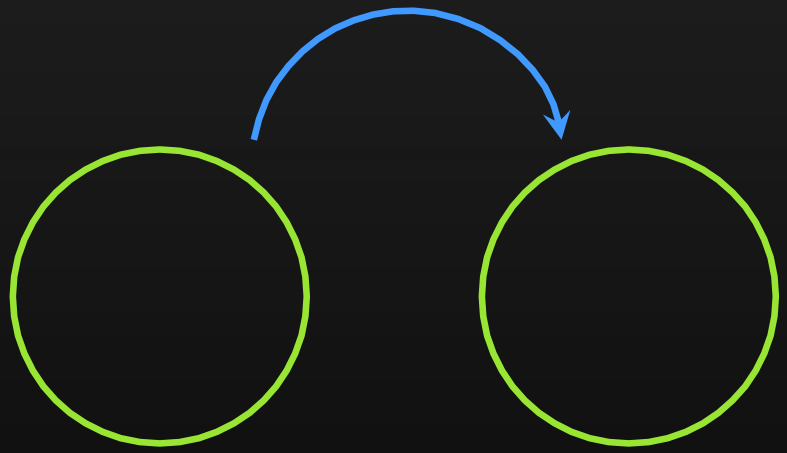
1

Skeletal muscle insulin resistance

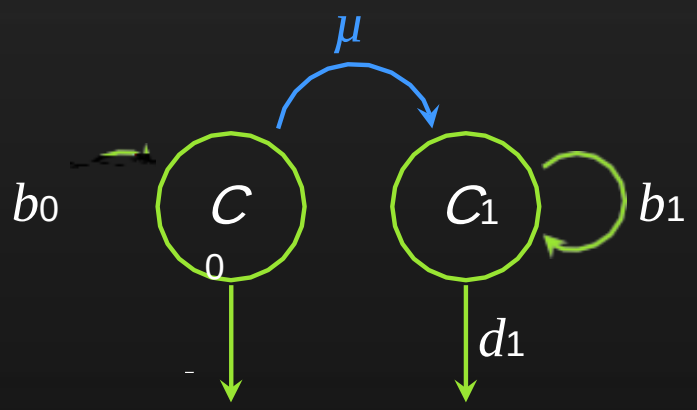
MARS: A network theory of aging

M
A
R





Modeling mitochondrial selection: setup



$M_0(t) :=$ C_0

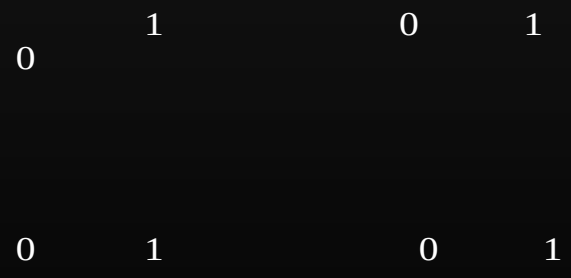
( )

–

the

Modeling mitochondrial selection: state transitions

	"	#	"
	M_0	1	-1
A	M_1	-1	1



Mean time to total damage

$T_i :=$ i

Superoxide-to-damage feedback

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

$$_j(t) := \Pr(M_1 \quad j)$$

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

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

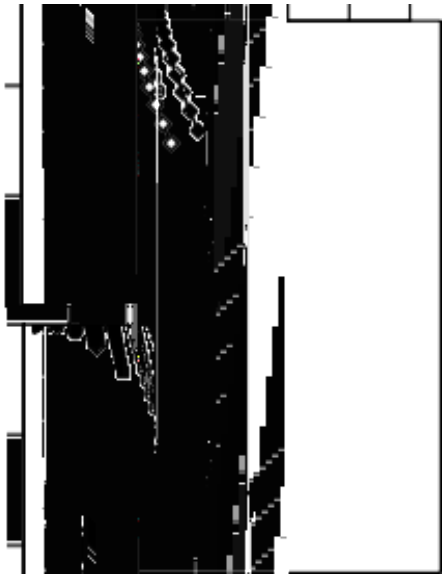
$$\frac{d\ _K}{dt} \quad \hat{q}_{K-1}\ _{K-1} \quad -\hat{p}_K\ _K$$

$$D(t) = \Pr(M_1 \geq 1) = \sum_{j=K}^{\infty} {}_j(t)$$

Feedback models I –

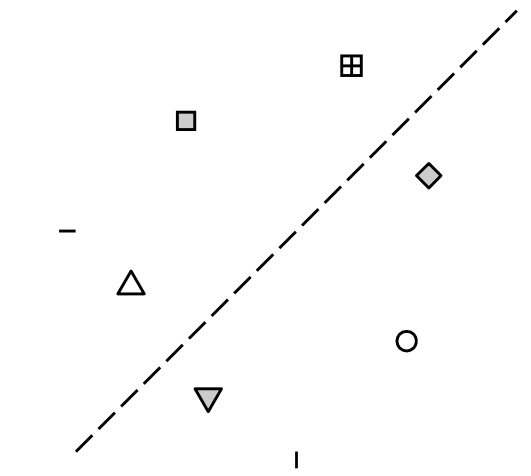
$$\mathrm{d}t$$

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

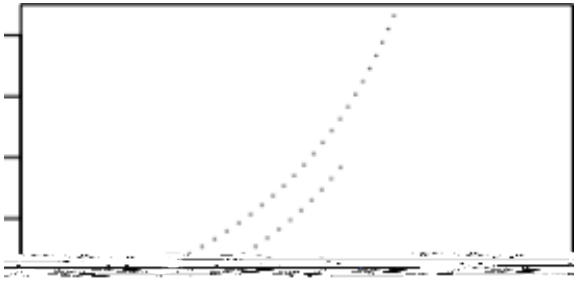


Superoxide

Results III: response to mitochondrial selection



Superoxide 10^5



Superoxide 10^5

Results IV: response to selection parameters