Dynamical Compensation and Mutant resistance in Tissues

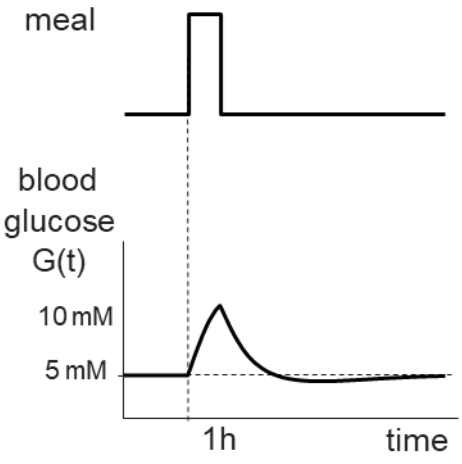
Challenges for Tissue:

1) Maintain size despite cell growth (even exponentially)
2) Signal precisely to other tissue (although their parameters are unknown)
3) Avoid mutant cells that might grow quicker and take over tissue

????????

Unifying circuit design can help here:

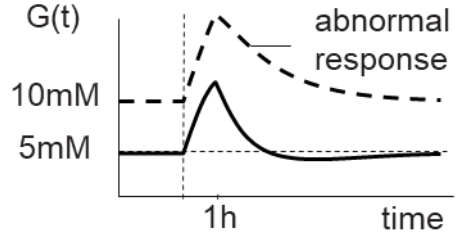
Example: Glucose -> Inulin regulation

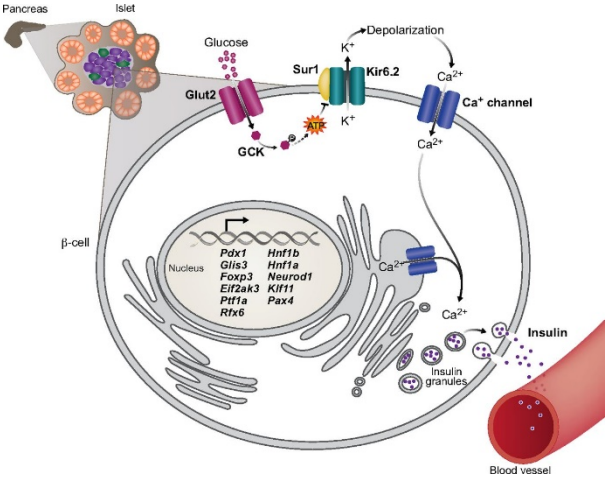


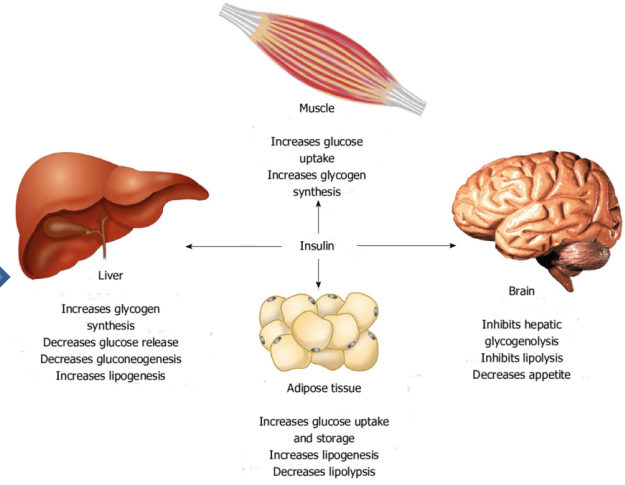
Glucose level very important:

- Too little -> unconsciousness or even death
- Too much: damage of vessels and organs (symptoms of Diabetes)

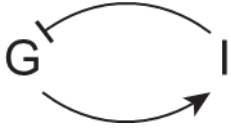
Glucose tolerance test G(t):





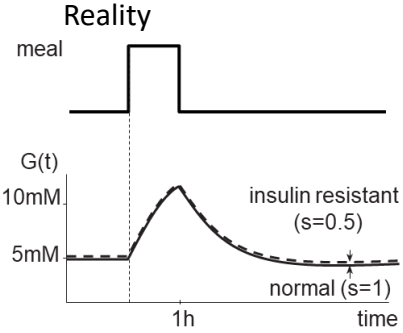


Negative feedback:



But: Large variation in insulin sensitivity s (factor 10!), still steady state always 5mM ???

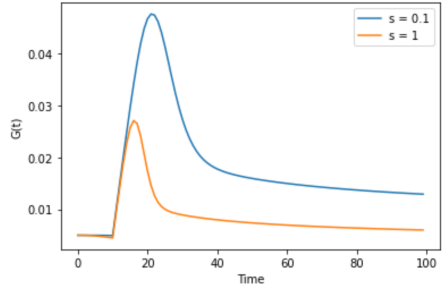
Puzzle: Why 5mM despite large variability in s?



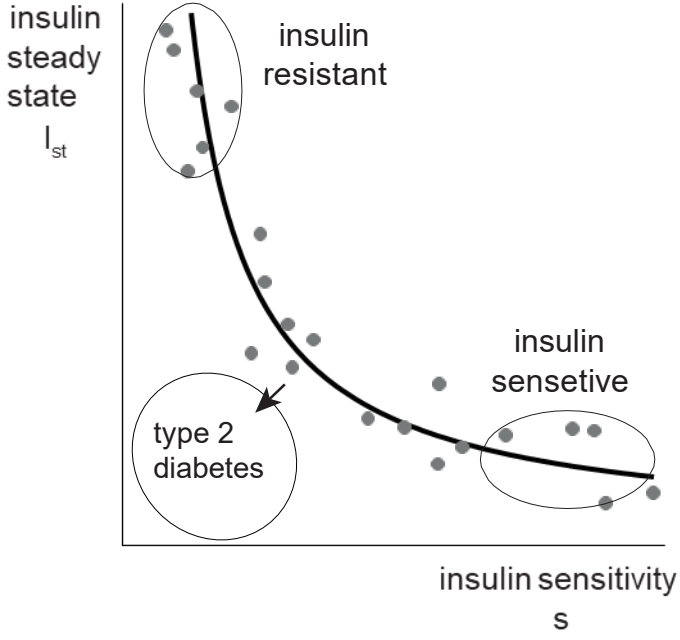
Solving with $f(G)=G^2$ does not work

```
q = 1

for i in range(n-1):
    G[i+1] = G[i] + m[i] - s*I[i]*G[i]
    I[i+1] = I[i] + q*B*f(G[i]) - g * I[i]

G1 = np.ones(n)*0.005
s = 1

for i in range(n-1):
    G1[i+1] = G1[i] + m[i] - s*I[i]*G1[i]
    I[i+1] = I[i] + q*B*f(G1[i]) - g * I[i]

plt.plot(G,label='s = 0.1')
plt.plot(G1,label='s = 1')
plt.legend()
plt.xlabel('Time')
plt.ylabel('G(t)')
```

[41]: `Text(0, 0.5, 'G(t)')`



Model does not work… what is going on?



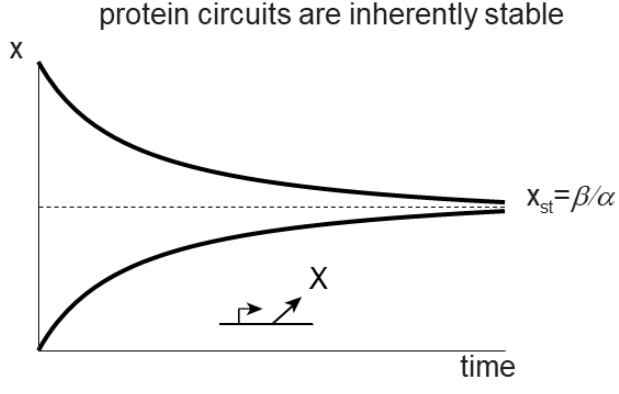
Body compensates with more \beta cells.

Hence simply with higher insulin steady state!

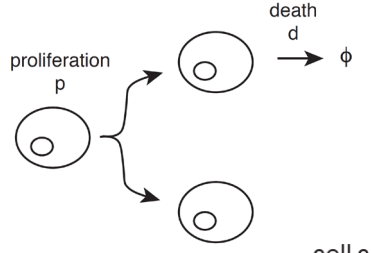
$$I_{st} * s = const$$

To model: Include number of B cells B(t) in model

We enter dynamics of cell populations

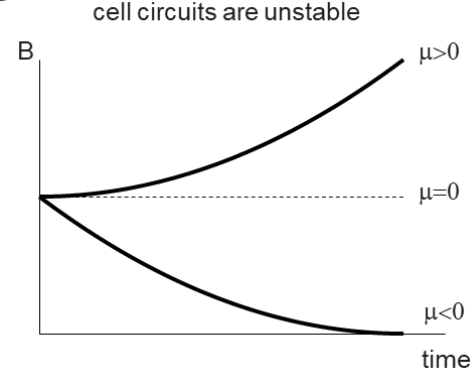


$$\frac{dx}{dt} = \beta - \alpha x$$



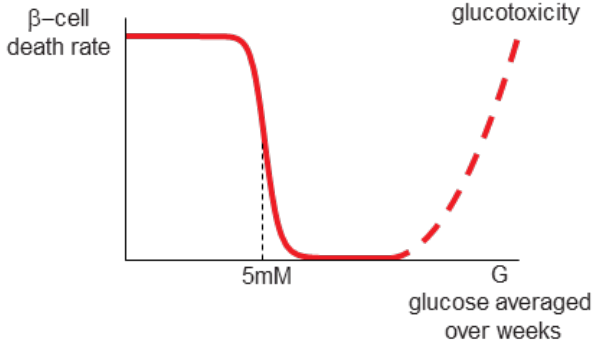
$$\frac{dB}{dt} = pB - dB = \mu B$$

With: $\mu = p - b$

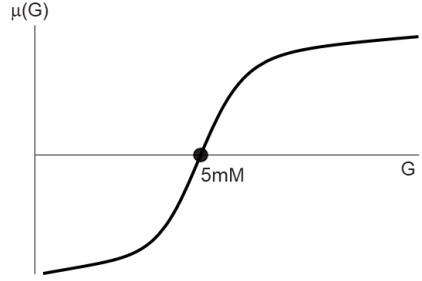


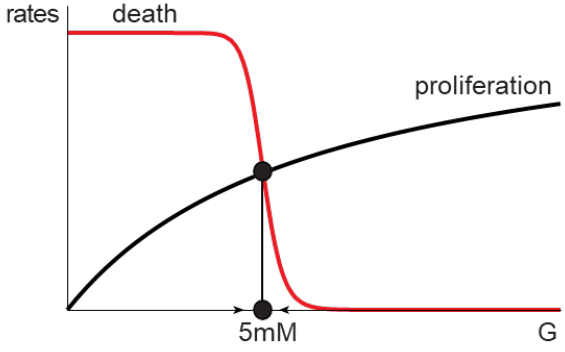
Problem: Tissue size control

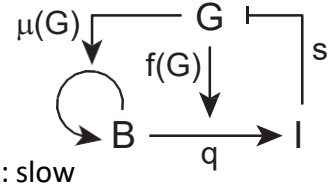
Cell proliferation and death needs to be controlled -> additional feedback



$$\mu = \mu(G)$$

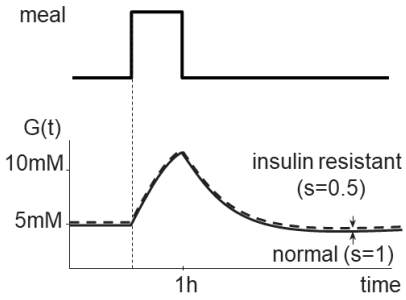






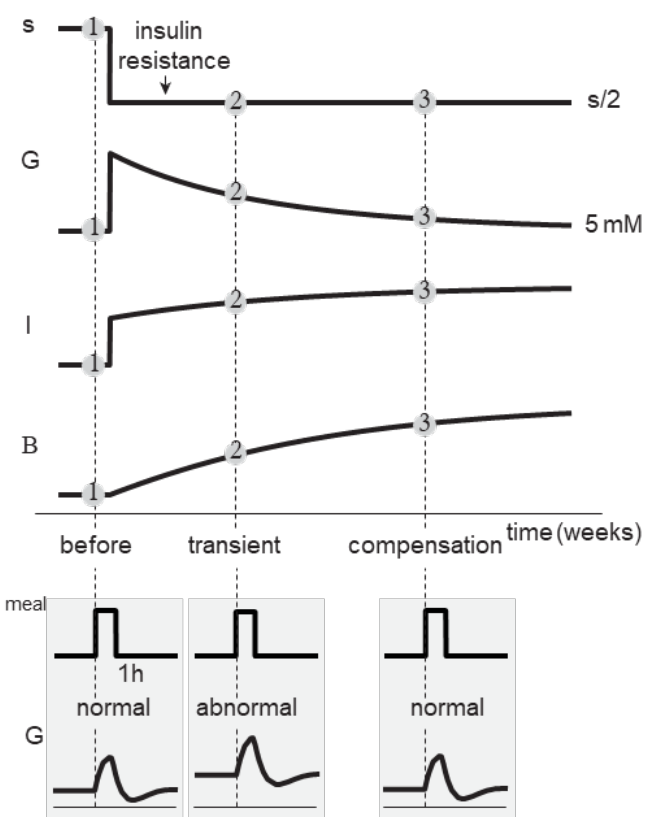
Proliferation: slow

Ok, this explain the 5mM, but there was more!

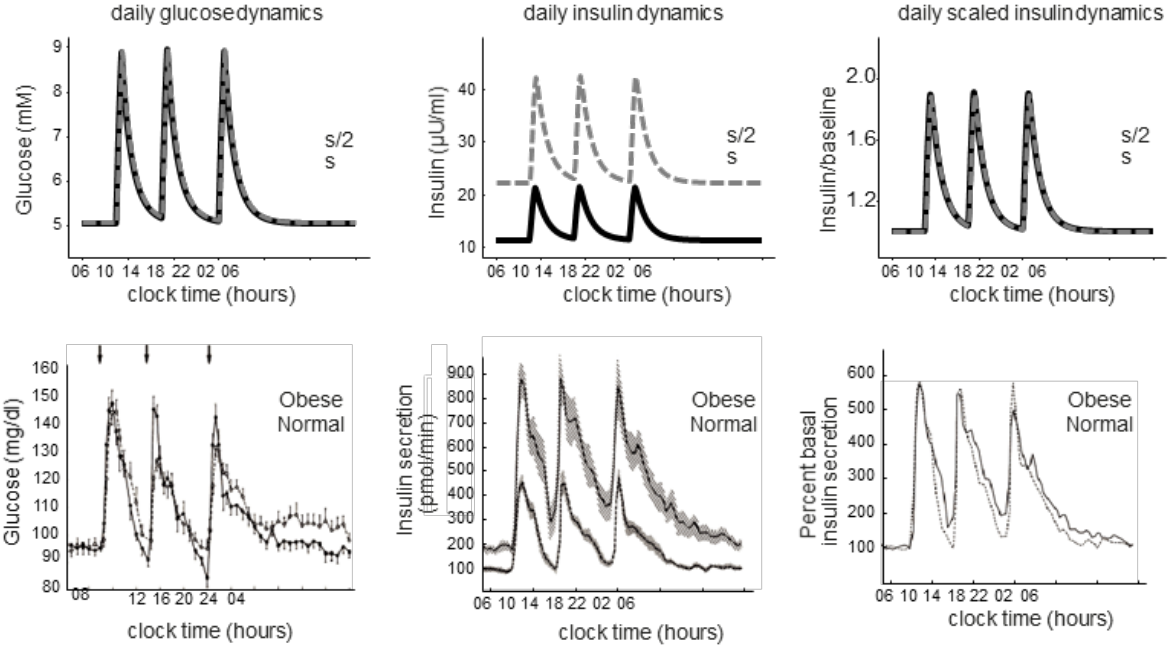


Dynamics independent of s!!!
(defined as Dynamical Compensation, DC)

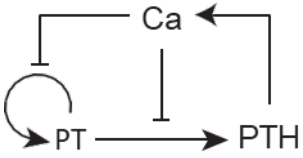
Rescaling can be used to show independence of equations

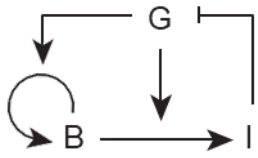

s
1
insulin
resistance
2
3
s/2
G
2
1
3
5 mM
I
2
3
1
B
3
2
1
time (weeks)
before
transient
compensation
meal
1h
normal
abnormal
normal
G

G shows DC, I is dependent on s

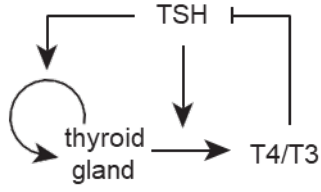


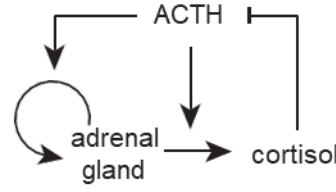
General feature of hormone systems from glands

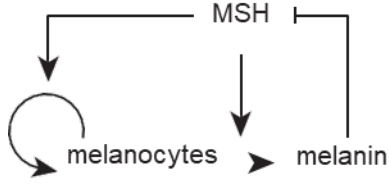


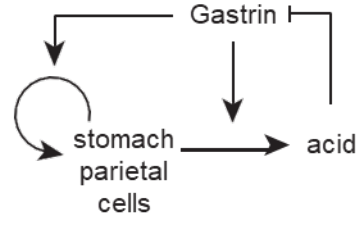


Calcium control via PTH

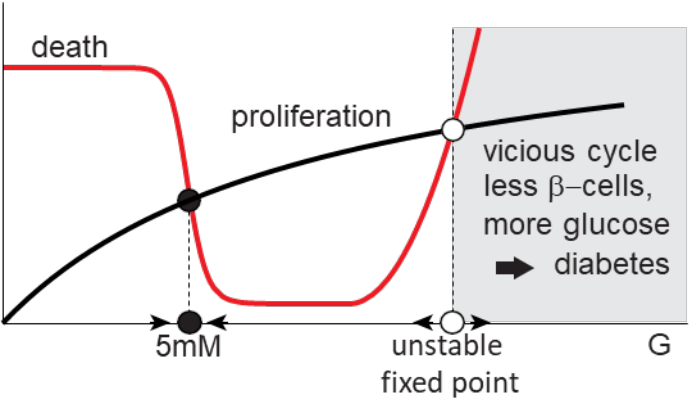






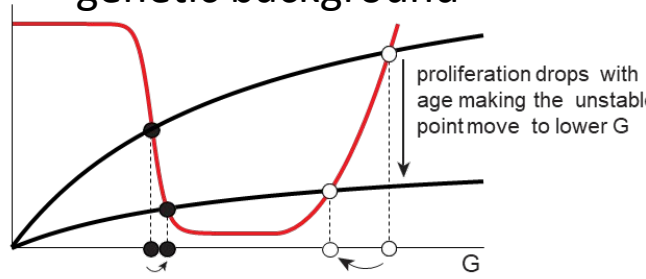


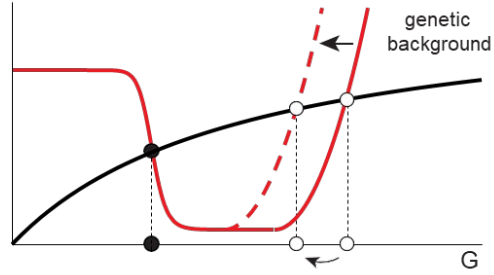
If the systems are so great why do the sometimes fail (Diabetes)?



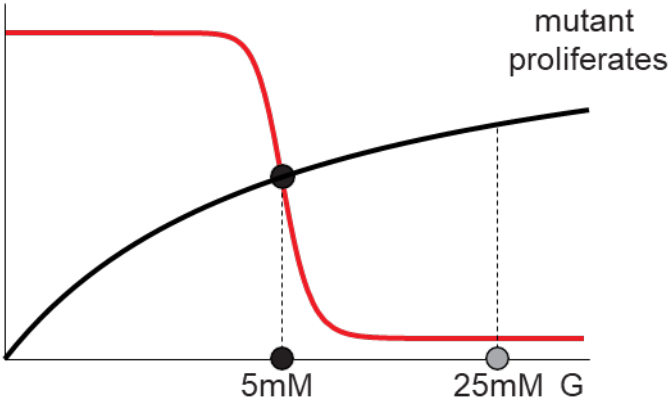
Type 2 diabetes: G too high -> death of \beta cells:

Risk: Age, high Glucose diet genetic background





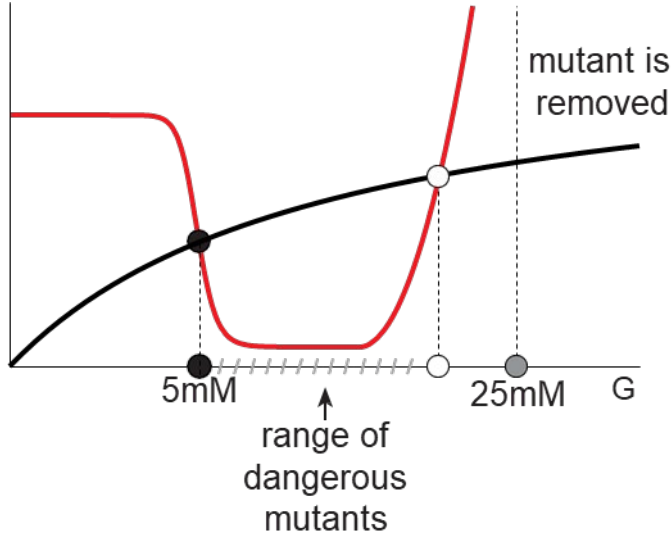
Possible role for Glycotoxisity: Avoid takeover by mutant cells



If mutation happens that detects G better

-> no cell death, but more division… mutation would win.

-> drastic increase of insulin, to little G -> death!



Biphasis reponse suppresses mutation: Neurotoxicity, immune cell toxicity with low and high antigens