Systems Medicine Lecture Notes

Uri Alon (Spring 2019)

https://youtu.be/gYtGgmbcDLE

Lecture 10

The growth axis, catch-up growth and Mini growth spurts

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Introduction:

In this lecture we will study the growth of children. Children grow rapidly in infancy, and growth velocity slows down and reaches an approximately constant velocity over childhood, with a final spurt at puberty (Fig 1). A remarkable feature of human growth is its **canalization**: although severe conditions in the uterus or infancy can permanently stunt growth, in most cases the final height is insensitive to childhood perturbations that slow down growth such as malnutrition and illness. Moreover, final height is insensitive to the random small fluctuations in conditions that life brings.

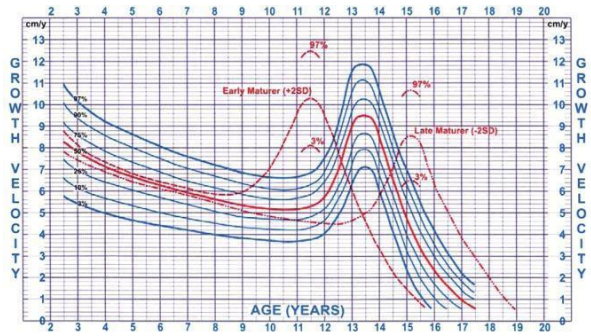

Figure 10.1

To see this canalization, we can plot the height **percentile** of a child relative to a reference population (Fig 2). Percentiles are useful because each population has different average height because of environment and genetics; percentiles are a good way to compare to the local reference population.

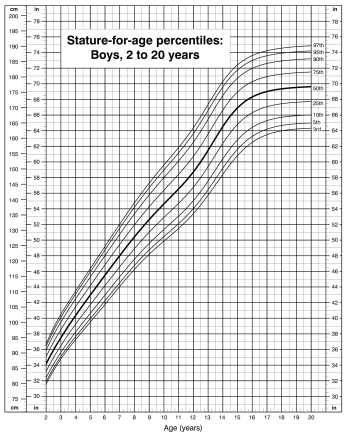

Figure 10.2

A healthy child's percentile is usually nearly constant- healthy children do not cross percentiles. This is canalization- it's as if the height curve follows a pre-set canal. A drop in a child's percentiles is an important indicator in pediatric medicine that something is wrong. In this lecture our main goal is to understand canalization of growth.

The constancy of percentiles is seen when measuring height every year or so. Growth, however, fluctuates on faster timescales. For example, measuring growth velocity accurately shows the phenomenon of **mini-growth spurts:** growth velocity oscillates with a period of 30-50 days (Fig 3). The origin of these spurts is a mystery that

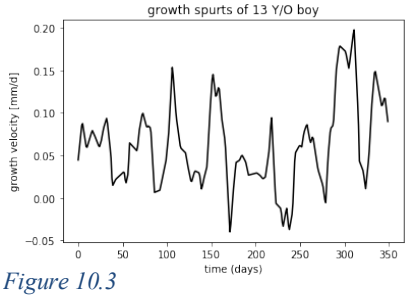

Figure 10.3

we will explain in this lecture. Growth velocity also shows seasonal changes and fluctuations due to infections and variations in nutrition and stress.

How is canalization achieved despite these variations? An extreme case occurs when there is severe growth retardation for a year or more. For example, children drop in percentiles when there is an undiagnosed illness such as celiac, hypothyroidism or Cushing's (high cortisol). Sometimes this drop is the way these diseases states are first detected. Growth can also be retarded due to malnutrition, which is unfortunately common in the world, or even severe psychological stress. The growth velocity drops, height stops growing.

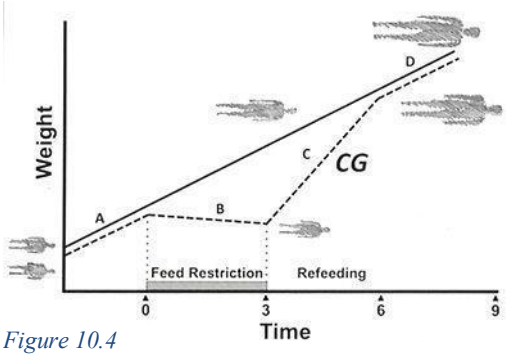

Figure 10.4

Importantly, growth resumes when the disease is diagnosed and treated, e.g. moving to non-gluten diet in the case of celiac, or improving nutrition in the case of malnutrition.

In principle, growth could just have continued at the same pace as appropriate for the age. But that is not the case. In most children, growth is up to 4 times faster than expected for their age. Height races up and often reaches the previous percentile (Fig 4). This is called **catch-up growth.** The growth system can thus

Sometimes catchup growth is only partial, and children don't reach their expected height, especially if puberty starts before catchup can be completed. Catchup growth is also found in animals (Fig 5).

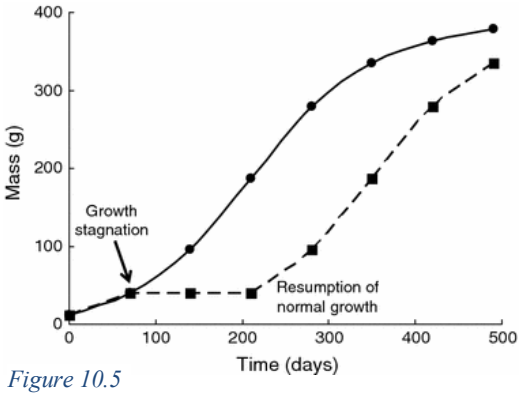

Figure 10.5

Two main theories for catchup growth

The origin of canalization and catch-up growth is unclear. There are two main theories: one in the brain and the other in the bone.

The first theory, by Tanner in 1972, is called the **sizostat** theory. It hypothesizes that there is a feedback circuit in the brain (a 'systemic' controller) that compares actual height to target height and corrects growth accordingly. A sizostat requires a setpoint - the desired growth velocity, a way to measure the current growth velocity and to compare it to the setpoint, and a way to accordingly produce a signal that affects growth velocity in order to correct it towards the setpoint. However, there is no known molecular implementation of such a sizostat.

The alternative theory is that catch-up growth is due to local mechanisms at the growth plate in the bones. To see this, we need to understand how growth of bones occurs. Height

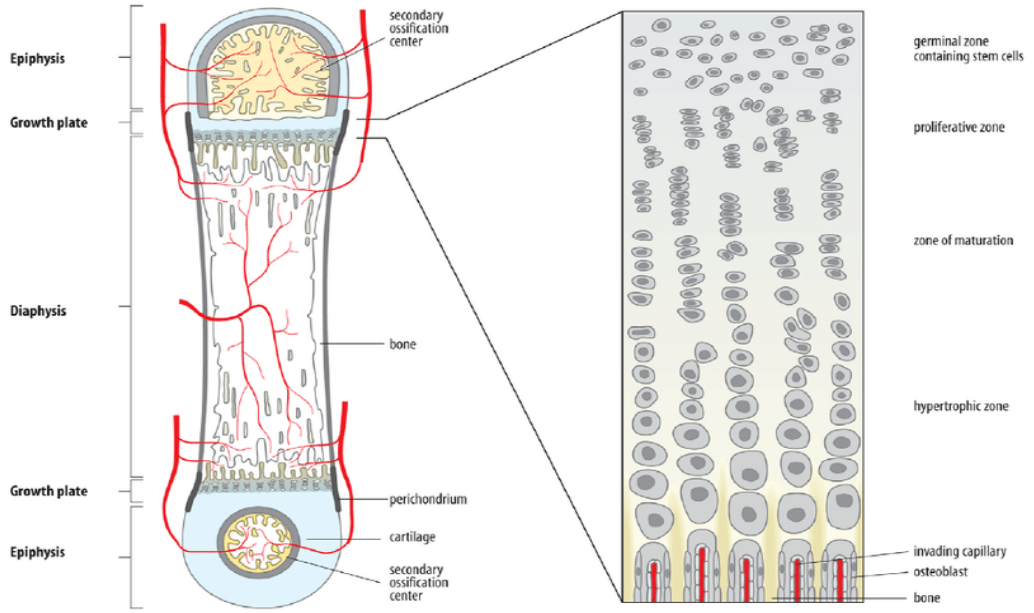

Figure 10.6

depends on the length of the long bones in the body. There are regions at both ends of each long bone called **growth plates** (Fig 6). They have a reserve of progenitor cells S, which differentiate into chondrocytes D, which proliferate about 30-fold, migrate down into the bone and enlarge in size to a length of about to $30\mu m$. The D cells then die and join the mineral part of the bone.

At puberty, estrogen makes the growth plates fuse, and growth stops- adult height is reached within a few years. One can tell the **bone age** by looking at the growth plates in the bones of the left hand.

The **growth plate theory** of catchup growth by Baron (1994) is that when growth is retarded, S cells don't turn into D cells. Instead they wait. This saves the store of S cells for when growth resumes. Thus, there is a finite number of S cells and that number is used up not as a function of time but as a function of differentiation events to D cells.

The growth rate theory is supported by an experiment that stopped growth in one limb of a rabbit. That limb showed partial catchup growth after the perturbation was removed. This means a local catchup process. Interestingly, the other limb also showed slightly accelerated growth, supporting a systemic mechanism in addition to the local one. More recent experiments indicate that the growth plate in animals shows more S cells during catchup than expected for that age.

The growth plate theory predicts a catchup growth velocity that is similar to the velocity at the age when the retardation started. Such catch up velocity is often seen. However, this theory cannot easily explain how growth sometimes resumes at a much faster rate.

Thus, it is currently believed that both a sizostat and a growth plate mechanism work together in catch-up. The big unknown is how a sizostat might be implemented in the body.

A sizostat in the growth hormone pathway

We will now see that a sizostat can be implemented by a hormonal circuit called the **growth axis.** The main idea is similar to that of lecture 4: gland sizes can grow and shrink over months and act as a memory element that can compensate for growth retardation.

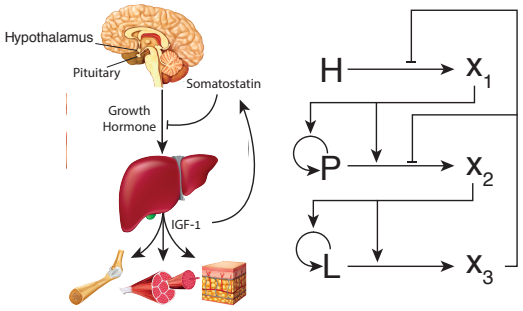

Figure 10.7

The growth axis has three hormones: x_1, x_2 and x_3 (Fig 7) secreted by three glands, H, P and L. The first gland H (hypothalamus) secretes the hormone x_1 (GHRH) that makes the cells in the second gland, P (pituitary somatotroph cells), secrete growth hormone x_2. Growth hormone affects the growth plate by making the S cells differentiate into D, as well as building muscle and enhancing metabolism (Fig 8). Along with its growth stimulating effects, growth hormone x_2 also makes the liver L secrete the third hormone, x_3 (IGF1). The x_3 hormone collaborates with x_2 to make bones grow by making the D cells in the growth plate proliferate and grow in size. As a detail, x_2 causes further local secretion of x_3 in the growth plate.

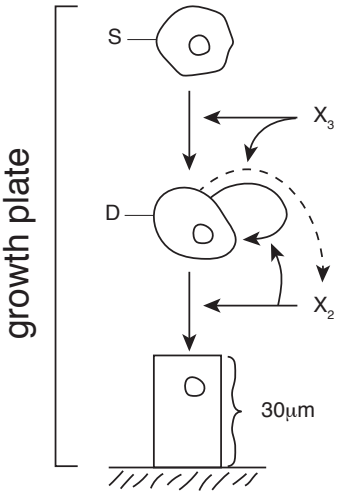

Figure 10.8

The hormone x_2 is an important growth factor for many cells in the body, and plays a key role in maintenance proliferation of cells in adults to provide the body's total for about 100g of cell turnover every day.

Mutations in x_2, x_3 or their receptors cause dwarfism. Tumors that hyper-secrete x_2 cause gigantism in children or acromegaly in adults, which causes problems due to overgrowth of bones.

As in the HPA axis of lecture 4, the hormone x_3 has a negative feedback loop by shutting down x_1 and x_2 production (Fig 7).

Thus, we can model hormone secretion using similar equations to those for the HA axis:

$$(1)\frac{dx_1}{dt} = \frac{b_1}{x_3} - a_1\, x_1$$

$$(2)\frac{dx_2}{dt} = b_2 P \frac{x_1}{x_3} - a_2\, x_2$$

$$(3)\frac{dx_3}{dt} = b_3\, L x_2^n - a_3\, x_3$$

the factor n in Eq.3 is due to the fact that the effect of GH on L is saturating (sublinear), and n~⅓. The input to the axis, in the hypothalamus, described here by b1, increases upon starvation and during sleep. The growth hormones are highest during sleep whereas cortisol, the hormone for activity, is highest during the day- allowing a division of labor between day time activity and nighttime growth and maintenance.

Since the hormones affect the growth plate, height velocity is an increasing function of x_2 and x_3:

$$\frac{dh}{dt} = w_2\, x_2 \; + w_3\, x_3$$

Where the weights w_2 and w_3 describe the effects of the hormones on the growth plates. If this was all, as in the textbooks, we cannot have a sizostat because this pathway has no memory beyond the lifetimes of the hormones, which is minutes to hours.

To add memory, we can use the fact that the glands sizes P and L are affected by their upstream hormones. x_1 causes P to grow, and x_2 causes L to grow (where 'grow' means increase the number and mass of the cells that secrete x_2 and x_3 respectively). The H gland is made of neurons and, like many neuronal brain regions, does not show cell turnover. The equations for the glands are a balance of cell divisions due to the upstream hormone and cell death, both proportional to the number of cells,

$$(4)\ \frac{dP}{dt} = b_P\, P(x_1 - a_P)$$
$$(5)\ \frac{dL}{dt} = b_L\, L(x_2 - a_L)$$

The timescales of the glands are much slower than the timescales of the hormones. The turnover time of P cells is about 60 days. The cells of the liver L have a slower turnover of about 300 days. The two glands thus have different half-lives, in contrast to the similar timescales of the two glands P and A in the HPA axis[1].

A first clue to the canalization of height is found when we calculate the steady state values of the hormones, to see that they depends on very few parameters: $x_{1_{st}} = a_P, \;\; x_{2_{st}} = a_L$ and from Equation (1), $x_{3_{st}} = \frac{b_1}{a_1} a_P$. Thus, if there are no perturbations and all parameters are constant over time, height goes as

$$h = w_2\, a_L\, t \; + \; w_3 \frac{b_1 a_P}{a_1}\, t$$

the weights w_2 and w_3 depend on may factors in the bone cell, and indeed height depends on nearly 1000 genes of small effect which add up height is about 80% heritable.

Now let's take a look at how the sizostat works in this model. The basic idea is that stress and disease suppress hormone secretion at the level of the P and L glands. As a result of the feedback circuit, these glands grow over months to compensate. This leaves enlarged glands when the perturbation is removed, providing a surge of growth hormones that lasts for months until the glands return to normal. This surge results in catch-up growth. Many stressful events, including psychological stress and prolonged inflammation, result in high cortisol which suppresses the production of x_1, x_2 and x_3 by acting on the cells in the H, P and L glands. Stress thus reduces b_1, b_2 and/or b_3. Adverse conditions and diseases can

[1] To avoid confusion, note that P in the growth axis and P in the HPA axis mean different cell populations within the pituitary: GH secreting cells called somatotrophs for the growth axis, and ACTH-secreting cells called corticotrophs for the HPA axis.

also lower the weights w_2 and w_3, to further suppress growth. We consider for simplicity the situation where w_2 and w_3 do not change over the time interval of interest.

Let's consider for example a typical case in which b_2 is reduced for a period of a year or two. Clinically, this can be due to hypothyroidism, since thyroid hormone enhances x_1 control of x_2 from P, and low thyroid causes growth retardation. As a result, x_2 drops in an hour or less. This makes x_3 drop as well. The drop in x_3 relieves the feedback inhibition on x_1 and thus x_1 rises. If gland sizes didn't change, the hormones would adjust to a new steady state for the within hours (Fig 9). After the stress is over, for example if the situation is diagnosed and thyroid hormone is given, b_2 returns to its normal value. The hormones quickly return to their previous steady-state. There is no catch-up growth.

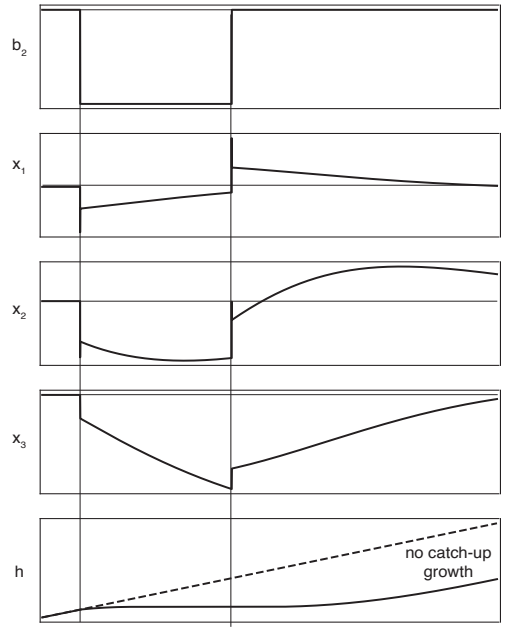

Figure 10.9

However, the dynamics of the gland sizes comes to the rescue (Fig 10). When b_2 drops, x_1 rises and as result, the P gland starts to grow over weeks. Similarly, L starts to shrink slightly over months.

When stress is relieved, P is larger than normal. There is a period of months in which x_2 and x_3 (GH and IGF1) secretion is high. As a result, growth velocity is high, causing catch up growth (Fig 10).

To see this mathematically, we can prove that for small perturbations, the loss of x_2 and x_3 during growth suppression is exactly equal to the gain after the stress is removed (Solved exercise 1). The size of the plus and minus lobes in Fig 10 is equal, and their area-under-the-curve cancels out. For large perturbations, simulations show that the compensation even provides more growth than needed for full catchup, perhaps to provide for the natural slowing down of growth as puberty is approached.

This sizostat works by using gland size as a memory element. Gland sizes change when the hormones are not at steady state, due to the integral feedback terms. For example, the equation $\frac{dP}{dt} = b_P\, P(x_1 - a_P)$ shows that the P gland size integrates over the error defined as the difference between the hormone and its set-point, $error = x_1 - a_P$. Rearranging the

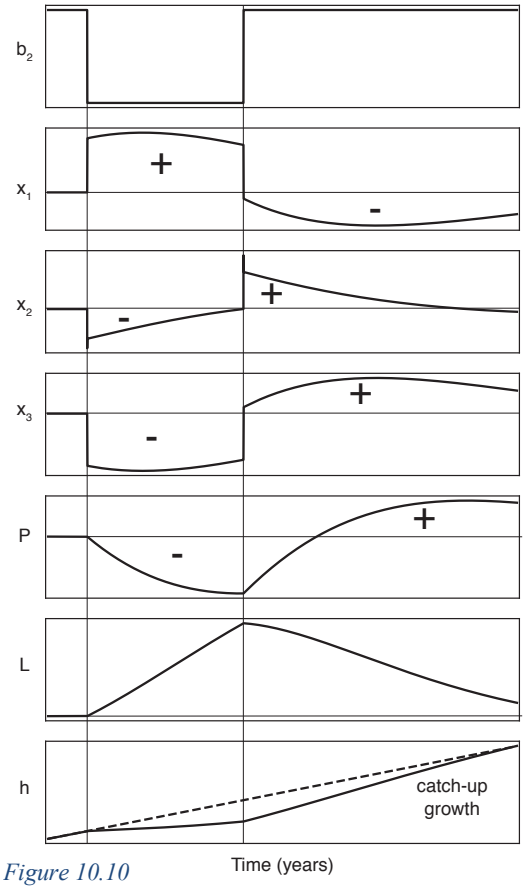

Figure 10.10

equation shows that $\log(P) \sim \int error(t)\, dt$. The glands store up information about the error between hormone levels and their set-point, and release this store when the perturbation is removed.

Mini growth spurts are caused by noise-induced oscillations in the two-gland feedback loop

The phenomenon of mini growth spurts, 30-50-day oscillations in height velocity in children, is well documented. In infants the oscillations are faster, with about a 10-day period. Mini growth spurts are also found in animals (rodents have a smaller period). Mini growth spurts are of no clinical importance, but we can use them to test the sizostat model.

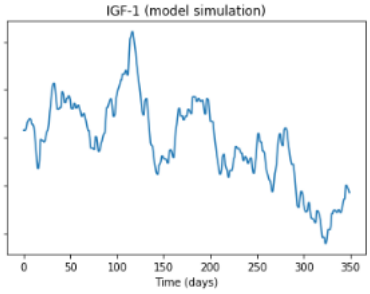

Figure 10.11

In the sizostat model we have an effective negative feedback loop between two glands, P and L, with lifetimes of 60 and 300 days (Fig 11). Thus, large P makes L grow which makes P shrink and so on, causing damped oscillations in gland sizes. This predicts, using linear theory, a spiral fixed point with a period of about $n\sqrt{(a_P a_L)}$~30 days.

Figure 10.12

Since life events, nutrition, infections etc. inevitably generate noise in this axis. When adding noise, the model shows noise-induced oscillations. the idea is the same as the truck with a spring-in-honey driving over a gravel road, as in lecture 4 (Fig 12). This generates mini growth spurts with rather precise period of about 30 days, but noisy amplitude, as observed.

One can also ask about seasonal oscillations. The L and P lifetimes predict that both x_2 and x_3 (GH and IGF1) have a late winter peak. To test this, we can use medical databases like Clalit (Lecture 4). Indeed, the predicted phases are found (Fig 13).

The growth axis thus shows a difference in seasonality from the other three HP axis: in those axes the pituitary hormones peak in summer, not winter. The reason for the difference is that in the other three pathways the turnover time of the cells in the P gland and the effector gland (adrenal,

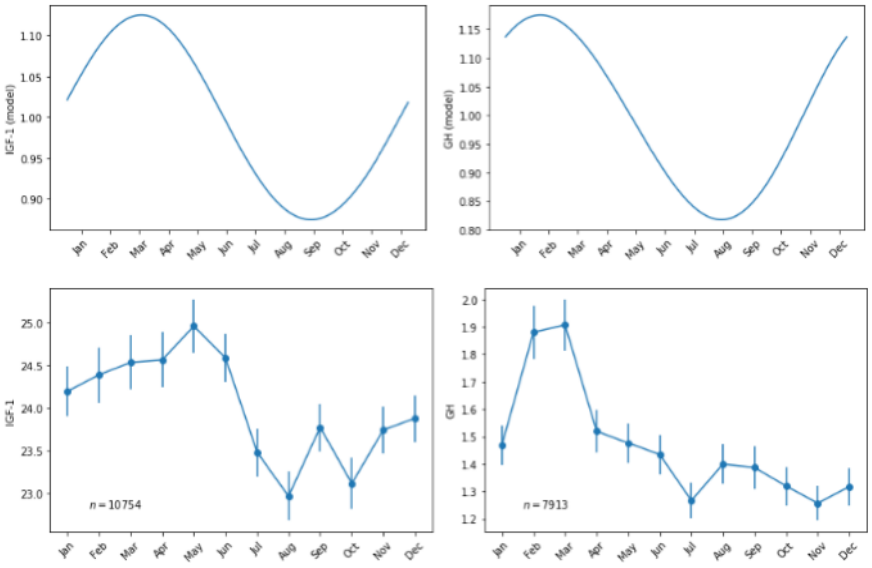

Figure 10.13

thyroid, ovaries/testes) is similar, whereas in the growth axis the effector organ (liver) has a much slower turnover than the P cells.

The sizostat can explain liver growth overshoots in transplants

Finally, this gland-oscillator comes into play in liver transplants. Liver transplant is a life-saving last resort for people with severe liver disease. A part of the liver is taken from a healthy donor and implanted in the patient, whose sick liver is removed. The donor liver grows back within a few months. The recipient shows liver growth that is faster and has an overshoot (Fig 14).

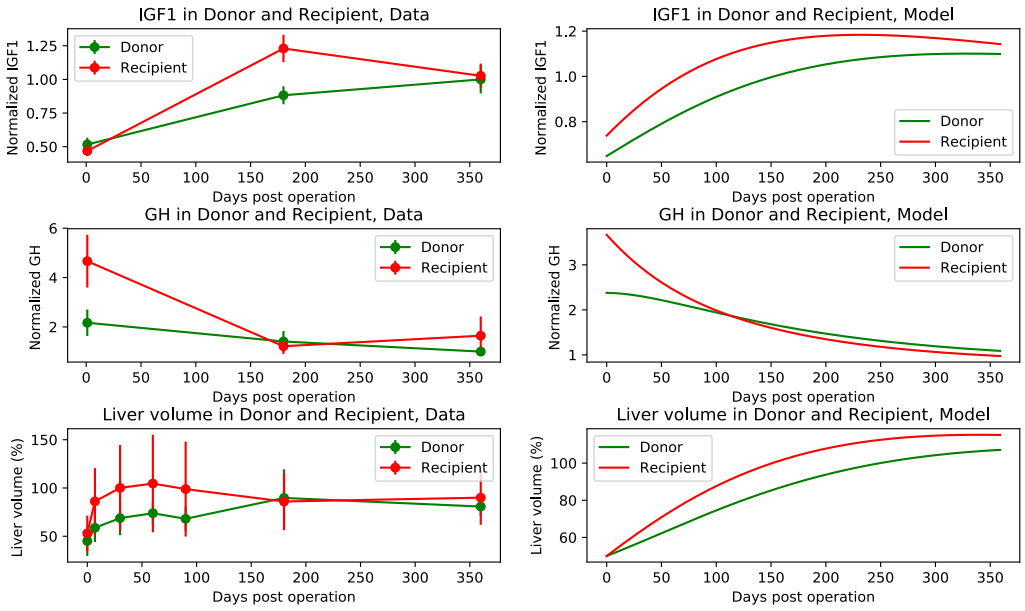

Figure 10.14

This overshoot is due to the enlarged P in the patient. The P gland is enlarged because in liver disease, the liver has impaired production of x_3. This alleviates the negative feedback on x1, making P grow. Indeed, liver disease often goes with high x_2 levels and low x_3 levels. Thus, the patient receives a good liver together with a lot of x_2, providing rapid and overshooting growth, which settles down once P returns to normal size.

In summary, the ability of the growth axis glands to change size can buffer growth fluctuations and keep growth trajectories along canalized routes. The height velocity of an individual is "written" in a few parameters such as the gland turnover times.

A major remaining mystery is what sets the timing of puberty? What timer can count 12-14 years? Sometimes, the stress that delays growth also delays puberty, giving more time for catch up growth. The body under stress makes cortisol, which reacts to the emergency by delaying non-urgent functions like growth, reproduction. Thus, cortisol suppresses the HP axes responsible for sexual maturity.

But what counts time up to 12 years for girls and 14 years for boys? What is the 'gonadostat'? we still don't know...

Exercises:

1. Show that for small perturbations, there is exact catchup growth in the model.

Solution: We will study the perturbation of x_3 from its steady state value by writing

$$x_3 = x_{3_{st}} + \delta x_3$$

We want to show that the area of the 'down lobe' in Fig 10 in which δx_3 is negative is exactly equal to that of the 'up lobe'. This equality of lobe areas means that the area under the curve is zero, $\int_0^T \delta x_3 dt = 0$. Here 0 is a time far before the growth perturbation, and T is a time long after, so that all variables including gland sizes return to their steady state value. If the areas under the lobes are equal for x_2 and x_3, final height is unperturbed, because the perturbation in final height is integral $w_2\ \delta x_2 + w_3\ \delta x_3\ dt$.

To see why the lobes have equal area, we will first separate x_1 into its steady state plus a perturbation, $x_1 = x_{1_{st}} + \delta x_1 = a_P + \delta x_1$ and show that $\int_0^T \delta x_1 dt = 0$, and then use that to show that $\int_0^T \delta x_3 dt = 0$

From Eq 4., $1/P\ dP/dt = x_1 - a_P$, or

$$(5)\ \frac{dlog(P)}{dt} = x_1 - a_p = \delta x_1 .$$

We now take the integral of both sides of the equation,

$$(6)\ \int_0^T \frac{dlog(P)}{dt}\ dt = \int_0^T \delta x_1\ dt$$

The integral over the derivative term is,

$$\int_0^T \frac{dlog(P)}{dt} = logP(T) - logP(0) = 0$$

Where we used the fact that $P(0) = P(T)$ because 0 is far before and T is far after the growth perturbation. Thus, using this in Eq. 6, we find

$$\int_0^T \delta x_1\ dt = 0.$$

The areas under the x_1 lobes are equal.

Now let's consider Eq. 1, which can be more generally written as

$$(6)\ \frac{dx_1}{dt} = f(x_3) - a_1\ x_1,$$

Let's assume δx_3 is small. We can expand around the steady state

$$f(x_{3_{st}} + \delta x_{3_{st}}) = f(x_{3_{st}}) + f'\ \delta x_3.$$

Thus, using that fact that at steady-state for Eq 6, $f(x_{3_{st}}) = a_1\ x_{1_{st}}$

$$\frac{dx_1}{dt} = f'(x_{3_{st}})\delta x_3 - a_1\ \delta x_1$$

Taking the integral over this equation yields

$$\int_0^T \frac{dx_1}{dt} dt = x_1(T) - x_1(0) = 0 = \int_0^T f'(x_{3_{st}})\delta x_3 - \int_0^T a_1 x_1\ dt.$$

And thus, because a_1 and $f'(x_{3_{st}})$ are constants, we have

$$\int_0^T \delta x_3 dt = \int_0^T x_1 \, dt = 0$$

Thus, the areas under the lobes of x_3 are equal. In the same way we can prove for the area under the x_2 lobes. We find that height is perfectly restored for small perturbations. It is almost perfectly restored (actually more than restored) in the nonlinear model.

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2. Analyze the sizostat when starvation causes an increase in b_1 and a large decrease in w_2 and w_3. Is there catchup growth?

3. x_3 is bound to carrier proteins in the blood (IGF binding proteins).

(a) Suppose the binding is very strong. Plot the amount of free (unbound) x_3 in the blood as a function of total x_3, assuming that binding protein level is B.
(b) How does this affect the sizostat? Suppose there is less x3 than B, how does the axis respond? Assume that only free x_3 participates in the growth axis feedback loop.
(c) Suppose that x_3 is made locally in the bone under control of x_2, but B is only made in the liver under control of x_2. Suppose further that a local growth perturbation in one growth plate inhibits the local production of x_2. How can this system provide information to the sizostat that a growth plate is inhibited?

4.

(a) Puberty stops growth, and comes earlier for girls; but girls are on average shorter than boys. Explain this.
(b) What might be an evolutionary rationale for puberty stopping growth?
(c) Drugs that interfere with sex hormones can delay puberty. How might these drugs be used in children whose growth was retarded due to a disease that can be treated?
(d) Growth hormone treatment works best on children whose x_2 was low. Explain.
(e) What is the effect of growth hormone treatment on the growth axis glands?
(f) How would you design an optimal treatment for increasing growth given the sizostat model, where you can provide x_2 and x_3 in pills?

5. **Catch down growth**: What do you expect will happen if a condition causes growth to be higher than the percentiles for a year or more, and then the condition stops?

6. In Laron dwarfism, the x_2 receptor is mutated. What would be the gland sizes and hormone levels?

Appendix

Let x_1, x_2 and x_3 be GHRH, GH and IGF1 concentrations, respectively. P and L are pituitary and liver functional mass (more precisely, P is the functional mass of somatotrophs that secrete GH and L is the functional mass of liver's hepatocytes)

The model equations are:

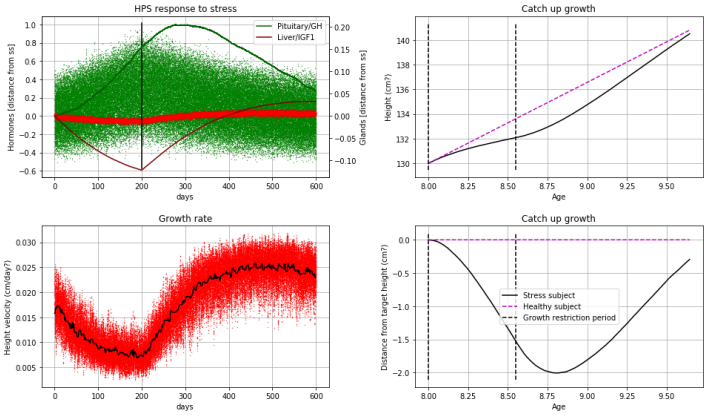
$$(1)\quad \frac{dx_1}{dt} = \frac{b_1 u}{x_3} - a_1 x_1$$

$$\frac{dx_2}{dt} = \frac{b_2 P x_1}{x_3} - a_2 x_2$$

$$\frac{dx_3}{dt} = b_3 L x_2^n - a_3 x_3$$

$$\frac{dP}{dt} = P(b_P x_1 - a_P)$$

$$\frac{dL}{dt} = L(b_L x_2 - a_L)$$



The values of the parameters, and the references for these values, are provided in table S1. As stated in the main text, the a_i parameters are the removal rates from the literature. We note here that this paper is focused on the slow timescale of weeks, and the rates a_1, a_2, a_3 do not affect many of the results on this timescale when using dimensionless variables.

Parameter	Value	Reference
a_1	$\frac{1}{6}[\frac{1}{min}]$	[get source of these values]
a_2	$\frac{1}{30}[\frac{1}{min}]$	"
a_3	$\frac{1}{110}[\frac{1}{min}]$	"
a_P	$\frac{1}{60}[\frac{1}{day}]$	"
a_L	$\frac{1}{300}[\frac{1}{day}]$	"
b_1	$\frac{1}{5}[\frac{1}{min}]$	Normalization of all variable steady-states to 1
b_2	$\frac{1}{30}[\frac{1}{min}]$	Normalization of all variable steady-states to 1
b_3	$\frac{1}{90}[\frac{1}{min}]$	Normalization of all variable steady-states to 1
b_P	$\frac{1}{60}[\frac{1}{day}]$	Normalization of all variable steady-states to 1
b_L	$\frac{1}{60}[\frac{1}{day}]$	Normalization of all variable steady-states to 1
n	$\frac{1}{3}$	"

Table S1. Values of parameters of the model used in this study.

Derivation of quasi-steady-state equations for the HPS model

The HPs model has two separable timescales, the timescale of minutes-hours of the hormones and the timescale of weeks for the glands. For the purpose of understanding the slow timescale, we can assume that the hormones reach quasi steady-state. We verified this by comparing the following analytical results to full simulations. We hence compute the quasi steady-state solution of the fast equations for a given gland functional mass P and L: *(3)*

$$0 = \frac{b_1 u}{x_3} - a_1 x_1$$
$$0 = \frac{b_2 P x_1}{x_3} - a_2 x_2$$
$$0 = b_3 L x_2^n - a_3 x_3$$

These equations are log-linear and have a unique solution for the hormone levels in terms of algebraic function of the gland sizes:
(4)

$$x_{1,qst} = \left(\frac{b_1^2 a_2 a_3}{a_1^2 b_2 b_3} u^2 P^{-n} L^{-1}\right)^{\frac{1}{2n+1}}$$
$$x_{2,qst} = \left(\frac{b_1 b_2 a_3^2}{a_1 a_2 b_3^2} u P L^{-2}\right)^{\frac{1}{2n+1}}$$
$$x_{3,qst} = \left(\frac{b_1 b_2 b_3}{a_1 a_2 a_3} u^n P^n L\right)^{\frac{1}{2n+1}}$$

Substituting the quasi-steady-state solution (Eq 4) of the hormones into the gland dynamic equations (1) gives two differential equations that operate on the slow timescale of weeks:
(5)

$$\frac{dP}{dt} = P(c_P u^{\frac{2}{2n+1}} P^{-\frac{n}{2n+1}} L^{-\frac{1}{2n+1}} - a_P)$$
$$\frac{dL}{dt} = L(c_L u^{\frac{1}{2n+1}} P^{\frac{1}{2n+1}} L^{-\frac{2}{2n+1}} - a_L)$$

Where $c_P = \left(\frac{b_1^2 a_2 a_3}{a_1^2 b_2 b_3}\right)^{\frac{1}{2n+1}} b_P$, $c_L = \left(\frac{b_1 b_2 a_3^2}{a_1 a_2 b_3^2}\right)^{\frac{1}{2n+1}} b_L$

In the case where we normalize the steady state of the variables to one we have $b_i = a_i$, therefore also $c_P = b_P = a_P$ and $c_L = b_L = a_L$.

This system of equation is a nonlinear negative feedback loop, in which P increases L and L inhibits P (Fig 1c).

Linear stability analysis of the steady state, and conditions for a spiral fixed point

The quasi state equations are a special case of:

(6)

$$\frac{dP}{dt} = P(c_P u^{n_{uP}} P^{n_{PP}} L^{n_{LP}} - a_P)$$
$$\frac{dL}{dt} = L(c_L u^{n_{uL}} P^{n_{PL}} L^{n_{LL}} - a_L)$$

If the system is nondegenerate, it has a nonzero fixed point:

(7)

$$P_{st} = \frac{c_P^2 a_L}{a_P^2 c_L} u, \;\; L_{st} = \frac{c_P c_L}{a_P a_L} u$$

To check the behavior around the fixed point, we compute the Jacobian, the matrix of derivatives at the fixed point:

(8)

$$\begin{pmatrix} \frac{d\dot{P}}{dP} & \frac{d\dot{P}}{dL} \\ \frac{d\dot{L}}{dP} & \frac{d\dot{L}}{dL} \end{pmatrix} = \begin{pmatrix} n_{PP} a_P & n_{LP} a_P \frac{P_{st}}{L_{st}} \\ n_{PL} a_L \frac{L_{st}}{P_{st}} & n_{LL} a_L \end{pmatrix}$$

To determine the stability of the fixed point we compute the determinant and trace:

(9)

$$det = a_P a_L (n_{PP} n_{LL} - n_{LP} n_{PL})$$
$$trace = a_P n_{PP} + a_L n_{LL}$$

In the HPS model, $n_{PP} = -\frac{n}{2n+1}, n_{LP} = -\frac{1}{2n+1}, n_{PL} = \frac{1}{2n+1}, n_{LL} = -\frac{2}{2n+1}$

Thus: $det > 0$ and $trace < 0$. Therefore, the fixed point is stable for any values of tissue turnover timescale a_P, a_A.

The fixed point is a spiral if $race^2 < 4det$. To determine the type of fixed point, we compute:

(10)

$$trace^2 - 4det = \frac{4a_R^2 \; + \; n^2 - 4(n+1)a_R}{(2n+1)^2}$$

Here, $a_R = a_L / a_P$ is the ratio between the timescale of the glands. In the HPL model, aR=1/5, n=1/3 and thus **the fixed point is spiral.**

Q factor is a dimensionless parameter that describes how underdamped an oscillator or resonator is. For the case of spiral fixed point, we can calculate the Q factor of this system.

The Q factor for a differential equation of a harmonic oscillator of the form

$$\ddot{X} + 2\zeta\omega_0\dot{X} + \omega_0^2 X = 0$$

Is

$$Q = \frac{1}{2\zeta}$$

In our case, the equation is of the form

$$\ddot{X} - Tr\dot{X} + detX = 0$$

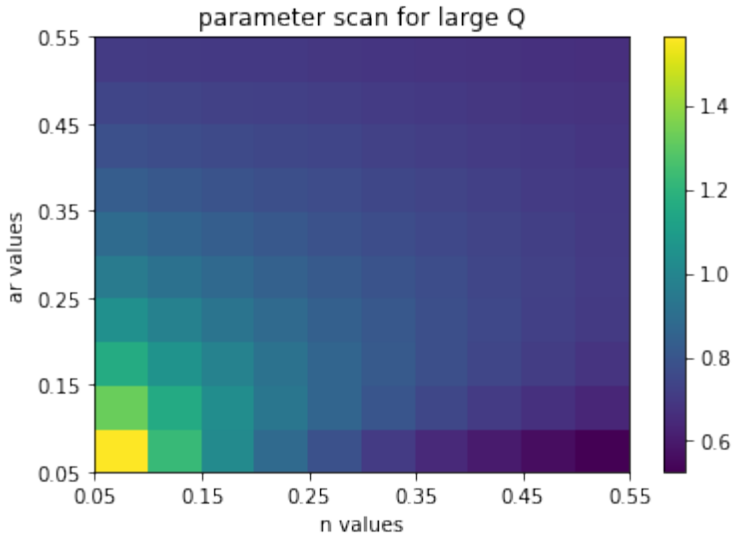
So

$$\omega_0 = \sqrt{det}$$

$$\zeta = \frac{-Tr}{2\omega_0} = \frac{-Tr}{2\sqrt{det}}$$

$$Q = \frac{-\sqrt{det}}{Tr}$$

In the HPL model, frequency is geometric mean of pituitary and liver times factor related to n, comes out as $1/omega = sqrt(60 * 300)/0.4$



Exercises

Catch-up growth for different parameters

In the lecture we introduced the HPS model:

$$\frac{dx_1}{dt} = \frac{b_1}{x_3} - a_1\, x_1$$
$$\frac{dx_2}{dt} = b_2 P \frac{x_1}{x_3} - a_2\, x_2$$
$$\frac{dx_3}{dt} = b_3\, L x_2^n\ - a_3\, x_3$$
$$\frac{dP}{dt} = b_P\, P(x_1 - a_P)$$
$$\frac{dL}{dt} = b_L\, L(x_2 - a_L)$$
$$\frac{dh}{dt} = w_2\, x_2\ + w_3\, x_3$$

We saw that if b_2 becomes smaller because of a disorder, we have a temporary reduction of growth (negative lobe of growth rate from the lecture). After the disorder is over and b_2 returns to its original value we get a positive lobe, whose area is equal to the negative one, this is catch-up growth.

In your simulations use the parameters:

$$b_1 = a_1 = b_2 = a_2 = b_3 = a_3 = 1\left[\frac{1}{day}\right]$$
$$a_P = a_L = 1$$
$$b_P = \frac{1}{60}[\frac{1}{day}]$$
$$b_L = \frac{1}{300}[\frac{1}{day}]$$
$$w_2 = \frac{1}{2}, w_3 = \frac{1}{2}$$
$$n = \frac{1}{3}$$

(A) Simulate catch-up growth. Run two simulations of the model, one with constant b_2, and another one with begin with the same b_2 , change the value to $\frac{b_2}{2}$ for 1 year and then back to b_2. Compare the simulations, and see the catch-up growth.

(B) If the change is in other parameters, do we still get catch-up growth? Repeat the simulations with b_3 changing instead of b_2. Do you still get catch-up growth? Can you intuitively understand why?

(C) Repeat it again with b_1. Now, do you get catch-up? Why?

Liver transplantation

In liver transplantation the donor donates a liver lobe to the recipient. After donation, the recipient liver regenerates faster than the donor liver. We explain this using the HPS model.

$$\frac{dP}{dt} = P(c_P u^{\frac{2}{2n+1}} P^{-\frac{n}{2n+1}} L^{-\frac{1}{2n+1}} - a_P)$$
$$\frac{dL}{dt} = L(c_L u^{\frac{1}{2n+1}} P^{\frac{1}{2n+1}} L^{-\frac{2}{2n+1}} - a_L)$$

(A) Simulate the donor liver trajectory. Use the HPS model with the initial conditions P=1 (healthy pituitary), L=1/2 (Half a liver).

(B) Compare the simulation above to the recipient liver trajectory, for the recipient use the initial conditions P > 1, L=1/2. Explain why these are the initial conditions for the recipient.

(C) Explain intuitively why recipient's liver regenerates faster than donor's liver.