PySB
rules and programming

Modeling bone microenvironment with PySB

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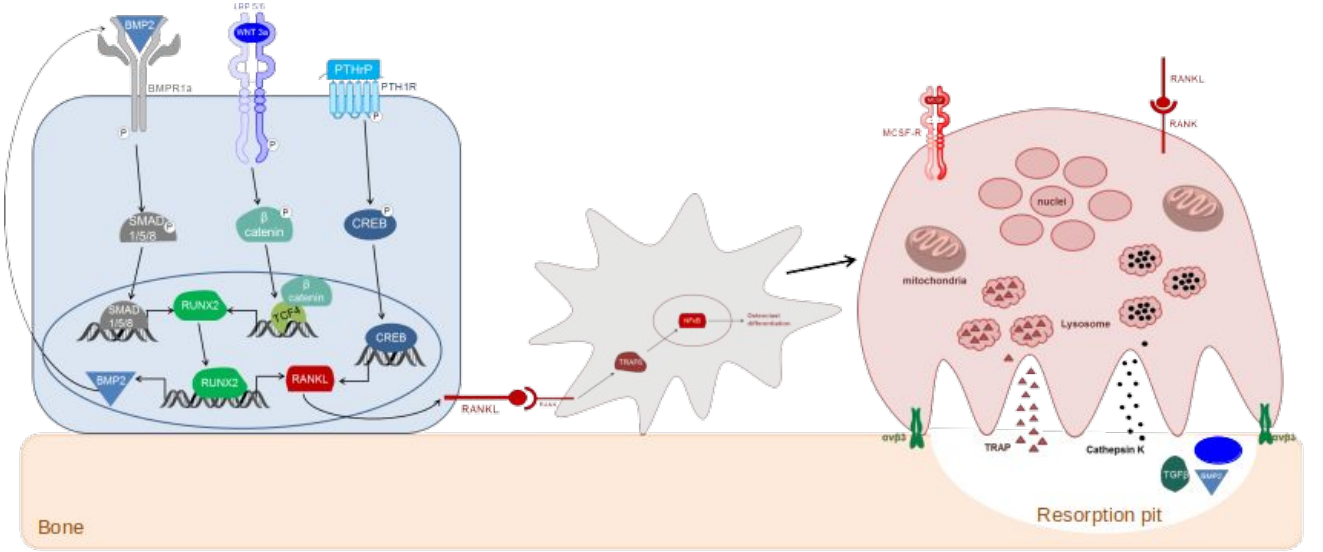
Under normal conditions, osteoblasts and osteoclasts are tightly regulated. Osteoclasts resorb areas of old bone, which releases factors that tell osteoblasts to come in and lay down new bone. Similarly, when osteoblasts lay down bone matrix, they signal to osteoclasts to come in and resorb bone. This results in an equilibrium and no net bone formation or loss in adults.

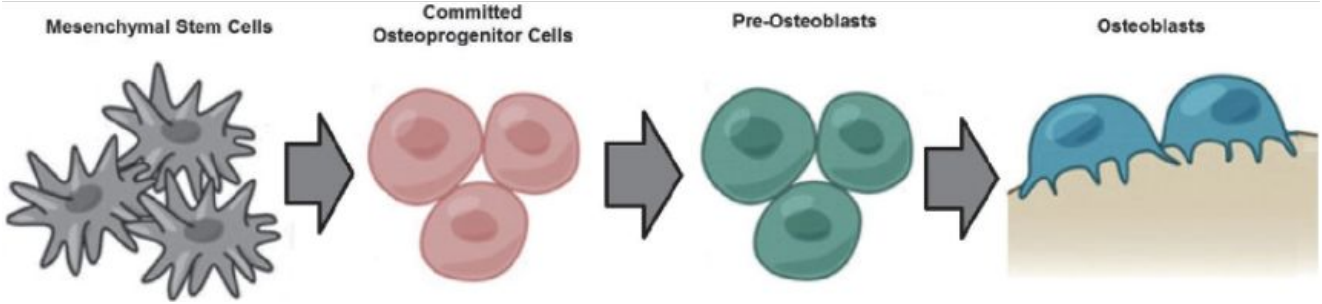
Slide by Alyssa Merkel, MS, Lab Coordinator, Medicine, Division of Clinical Pharmacology, Vanderbilt University

Participants in the bone-cycle

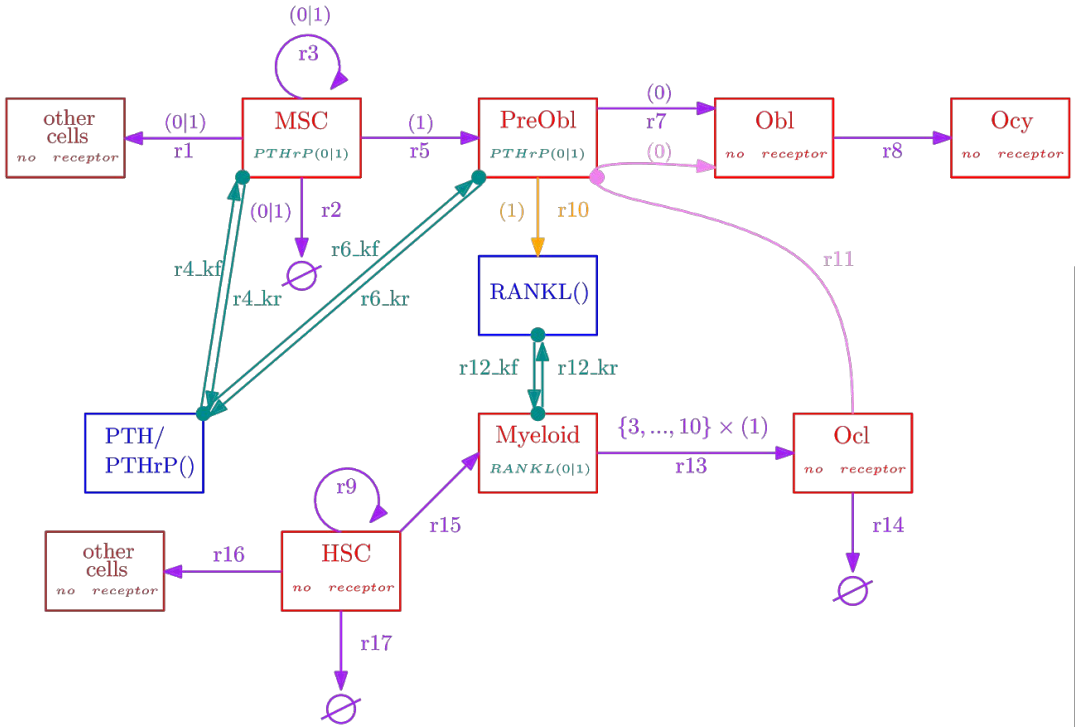
- Mesenchymal stem cells (MSC) use the PTH/PTHrP proteins to differentiate into PreOsteoblasts
- PreOsteoblasts can turn into Osteoblasts or express with PTH/PTHrP RANKL (a RANK ligand)
- Myeloids are introduced by the Hematopoietic stem cells (HSC) into the system and use RANKL to form Myeloid chains
- A Myeloid-chain of the size of {3,4,...,10} links can differentiate into Osteoclasts

- Osteoblasts create bone; when they transform into Osteocytes, they are basically dead to the system
- Osteoclasts destroy bone
- A healthy human bone-cycle is basically, when Osteoblasts and Osteoclasts are in equilibrium





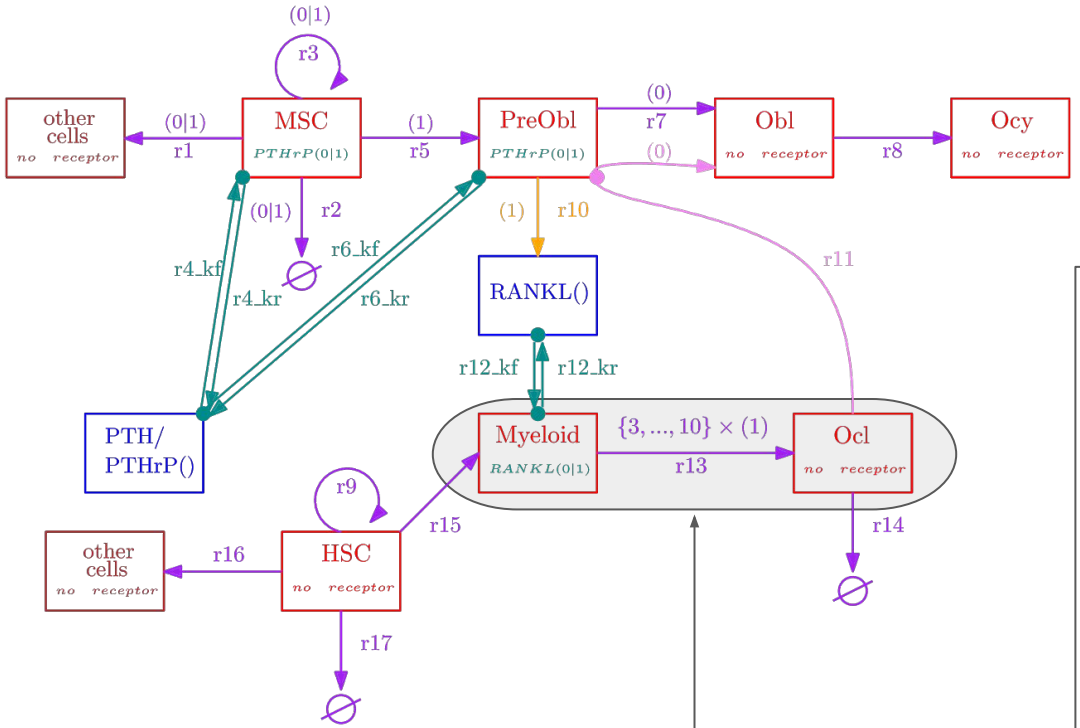
Slide by Alyssa Merkel, MS, Lab Coordinator, Medicine, Division of Clinical Pharmacology, Vanderbilt University



red … cells
blue … proteins

purple … cell ways
green … protein docking
orange … ligand expression
violet … feedback for additional Obl production triggered by the number of Ocl in the system

parenthesis
0 … receptor empty
1 … receptor bound



How to implement?

red … cells
blue … proteins

purple … cell ways
green … protein docking
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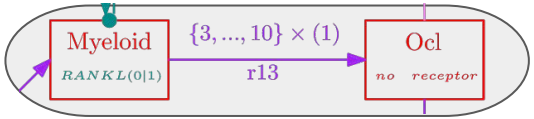

Resulting rules for the Myeloid-chain formation and the differentiation into Osteoclasts

```
Rule('bind_two_Myeloids',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=None),r13_kf,r13_kr)

Rule('bind_Myeloids_n3',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_3_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n4',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=None) +
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
    %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_4_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n5',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
      Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_5_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n6',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
    %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
    %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_6_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n7',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=None) +
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_7_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n8',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_8_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n9',
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     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=None) + Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=8)%Myeloid(RANKL_receptor=ANY,cell_docl=8,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_9_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=8)%Myeloid(RANKL_receptor=ANY,cell_docl=8,cell_docr=None) >> Osteoclast(),r13_ocl)

Rule('bind_Myeloids_n10',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=8)%Myeloid(RANKL_receptor=ANY,cell_docl=8,cell_docr=None) +
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=None) |
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=8)%Myeloid(RANKL_receptor=ANY,cell_docl=8,cell_docr=9)
     %Myeloid(RANKL_receptor=ANY,cell_docl=9,cell_docr=None),r13_kf,r13_kr)
Rule('Ocl_by_10_Myeloid_chain',
     Myeloid(RANKL_receptor=ANY,cell_docl=None,cell_docr=1)%Myeloid(RANKL_receptor=ANY,cell_docl=1,cell_docr=2)%Myeloid(RANKL_receptor=ANY,cell_docl=2,cell_docr=3)
     %Myeloid(RANKL_receptor=ANY,cell_docl=3,cell_docr=4)%Myeloid(RANKL_receptor=ANY,cell_docl=4,cell_docr=5)%Myeloid(RANKL_receptor=ANY,cell_docl=5,cell_docr=6)
     %Myeloid(RANKL_receptor=ANY,cell_docl=6,cell_docr=7)%Myeloid(RANKL_receptor=ANY,cell_docl=7,cell_docr=8)%Myeloid(RANKL_receptor=ANY,cell_docl=8,cell_docr=9)
     %Myeloid(RANKL_receptor=ANY,cell_docl=9,cell_docr=None) >> Osteoclast(),r13_ocl)
```

Use the power of programming

Note that the differentiation of Myeloids into Osteoclasts happens in various different ways: a Myeloid chain of 3, 4, … 10 links can form one Osteoclast. The maximum number (in our case 10) is variable in the code.

To avoid writing 10 (or even a variable number of) different rules (see previous slide) we used loops and dictionaries provided by Python: the object *myeloid_chain(n=10)* is similar to a function in programming, where n is the parameter which determines the maximum number of chain links for an Osteoclast.

leftmost_reaction is a dictionary of the form Myeloid(left_receptor=None,right_receptor=1)

inner_links is a dictionary containing the Myeloids between the left- and rightmost- link
M(lr=1,rr=2)%M(lr=2,rr=3)%...%M(lr=n-2,rr=n-1) created by looping over the dictionary and appending *%(lr=i+1,rr=i+2)* during loop cycle

rightmost_reactions is a dictionary that contains a reaction of the form *M(lr=i,rr=None)*, $i \in \{1,...,n\}$

using loops, the chains can now be concatenated by *leftmost_reaction[0]%inner_links[i-1]%rightmost_reactions[i]*, $i \in \{1,...,n-1\}$

The PySB rules use now the concatenated entries from the reaction chain.

System of ODEs generated by the model (23)

```
__s0*r3 + __s4*r3 + __s4*r4_kr + (__s0*r1)*(-1) + (__s0*r2)*(-1) + (__s0*__s2*r4_kf)*(-1)
__s1*r9 + (__s1*r15)*(-1) + (__s1*r16)*(-1) + (__s1*r17)*(-1)
__s4*r4_kr + __s7*r6_kr + (__s0*__s2*r4_kf)*(-1) + (__s2*__s8*r6_kf)*(-1)
__s0*r1 + __s4*r1
__s0*__s2*r4_kf + (__s4*r1)*(-1) + (__s4*r2)*(-1) + (__s4*r4_kr)*(-1) + (__s4*r5)*(-1)
__s1*r15 + __s11*r12_kr + (__s5*__s9*r12_kf)*(-1)
__s1*r16
__s2*__s8*r6_kf + __s4*r5 + (__s7*r6_kr)*(-1)
__s7*r6_kr + (__s8*r7)*(-1) + (__s15*__s8*r11)*(-1) + (__s2*__s8*r6_kf)*(-1)
__s11*r12_kr + __s7*r10 + (__s5*__s9*r12_kf)*(-1)
__s15*__s8*r11 + __s8*r7 + (__s10*r8)*(-1)
__s14*r13_kr + __s16*r13_kr + __s17*r13_kr + __s18*r13_kr + __s19*r13_kr + __s20*r13_kr + __s21*r13_kr
          + __s22*r13_kr + __s5*__s9*r12_kf + (__s11*r12_kr)*(-1) + (__s11**2*r13_kf)*(-2) + (__s13*r13_kr)*2
          + (__s11*__s13*r13_kf)*(-1) + (__s11*__s14*r13_kf)*(-1) + (__s11*__s16*r13_kf)*(-1)
          + (__s11*__s17*r13_kf)*(-1) + (__s11*__s18*r13_kf)*(-1) + (__s11*__s19*r13_kf)*(-1)
          + (__s11*__s20*r13_kf)*(-1) + (__s11*__s21*r13_kf)*(-1)
__s10*r8
__s11**2*r13_kf + __s14*r13_kr + (__s13*r13_kr)*(-1) + (__s11*__s13*r13_kf)*(-1)
__s11*__s13*r13_kf + __s16*r13_kr + (__s14*r13_kr)*(-1) + (__s14*r13_ocl)*(-1) + (__s11*__s14*r13_kf)*(-1)
__s14*r13_ocl + __s16*r13_ocl + __s17*r13_ocl + __s18*r13_ocl + __s19*r13_ocl + __s20*r13_ocl + __s21*r13_ocl
          + __s22*r13_ocl + (__s15*r14)*(-1)
__s11*__s14*r13_kf + __s17*r13_kr + (__s16*r13_kr)*(-1) + (__s16*r13_ocl)*(-1) + (__s11*__s16*r13_kf)*(-1)
__s11*__s16*r13_kf + __s18*r13_kr + (__s17*r13_kr)*(-1) + (__s17*r13_ocl)*(-1) + (__s11*__s17*r13_kf)*(-1)
__s11*__s17*r13_kf + __s19*r13_kr + (__s18*r13_kr)*(-1) + (__s18*r13_ocl)*(-1) + (__s11*__s18*r13_kf)*(-1)
__s11*__s18*r13_kf + __s20*r13_kr + (__s19*r13_kr)*(-1) + (__s19*r13_ocl)*(-1) + (__s11*__s19*r13_kf)*(-1)
__s11*__s19*r13_kf + __s21*r13_kr + (__s20*r13_kr)*(-1) + (__s20*r13_ocl)*(-1) + (__s11*__s20*r13_kf)*(-1)
__s11*__s20*r13_kf + __s22*r13_kr + (__s21*r13_kr)*(-1) + (__s21*r13_ocl)*(-1) + (__s11*__s21*r13_kf)*(-1)
__s11*__s21*r13_kf + (__s22*r13_kr)*(-1) + (__s22*r13_ocl)*(-1)
```

Exercise

In the provided notebook, we implemented the chemical reaction model as depicted in the previous slide. All rates (r1 - r15) have been set to 1.0. The system starts with 1 unit of MSC, 1 unit of HSC, and 100 units of PTH/PTHrP (the number of PTH/PTHrP in this system stays constant over time).

- Play around with the various rates - can you find a combination in which the Osteoblasts and Osteoclasts are in a (non-zero) equilibrium? (Note that it only makes sense to change rates in order of magnitude, i.e. 0.01, 0.1, 1.0, 10.0, 100.0,...)
- Paget’s disease is a bone disease which is associated with a mutation in the RANK. In our model, this means that Myeloids are lacking a proper receptor for RANKL. How does a change in this connection (r12_kf) affect a healthy system?