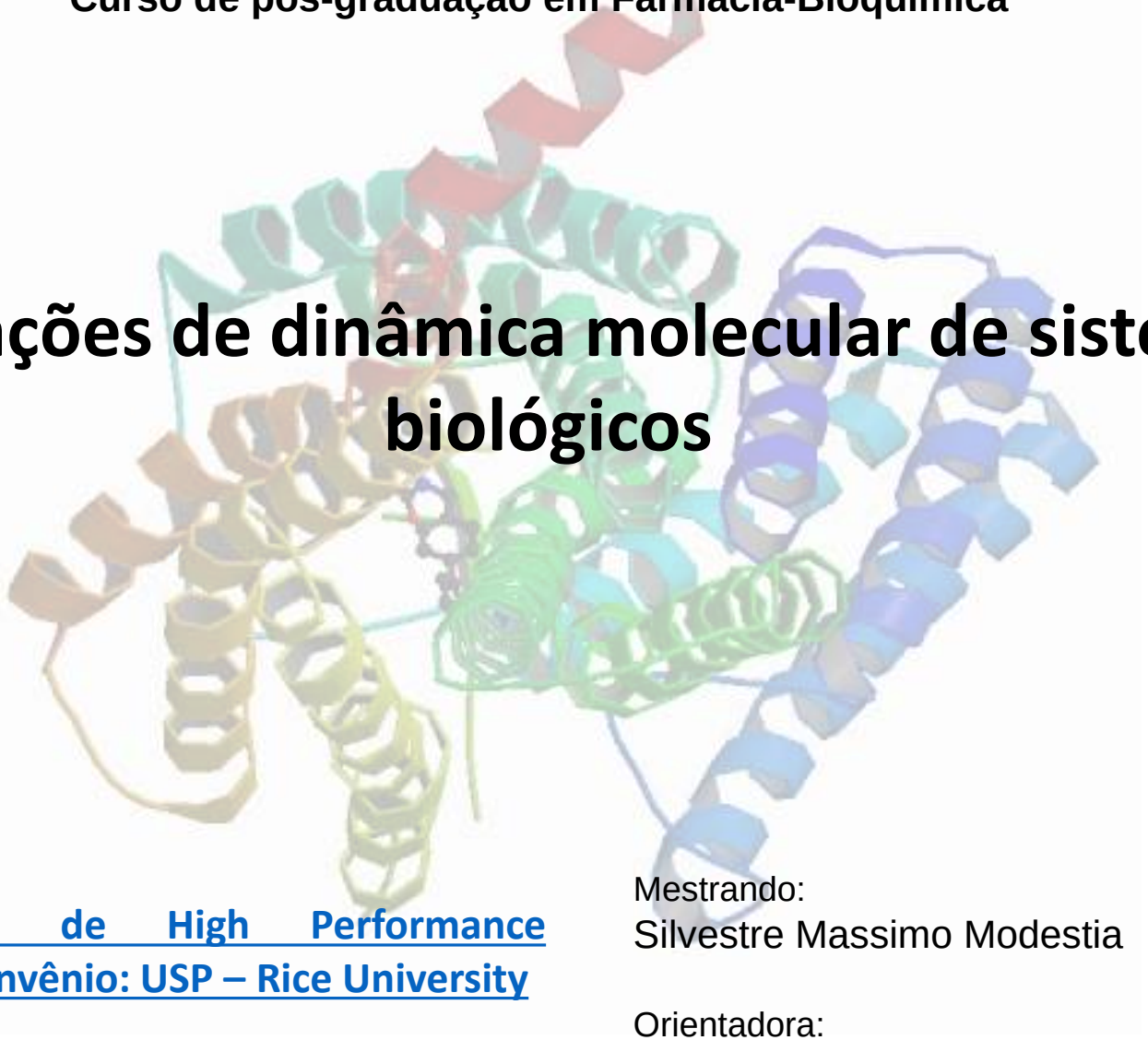
UNIVERSIDADE DE SÃO PAULO
FACULDADE DE CIÊNCIAS FARMACÊUTICAS
Curso de pós-graduação em Farmácia-Bioquímica

Simulações de dinâmica molecular de sistemas biológicos



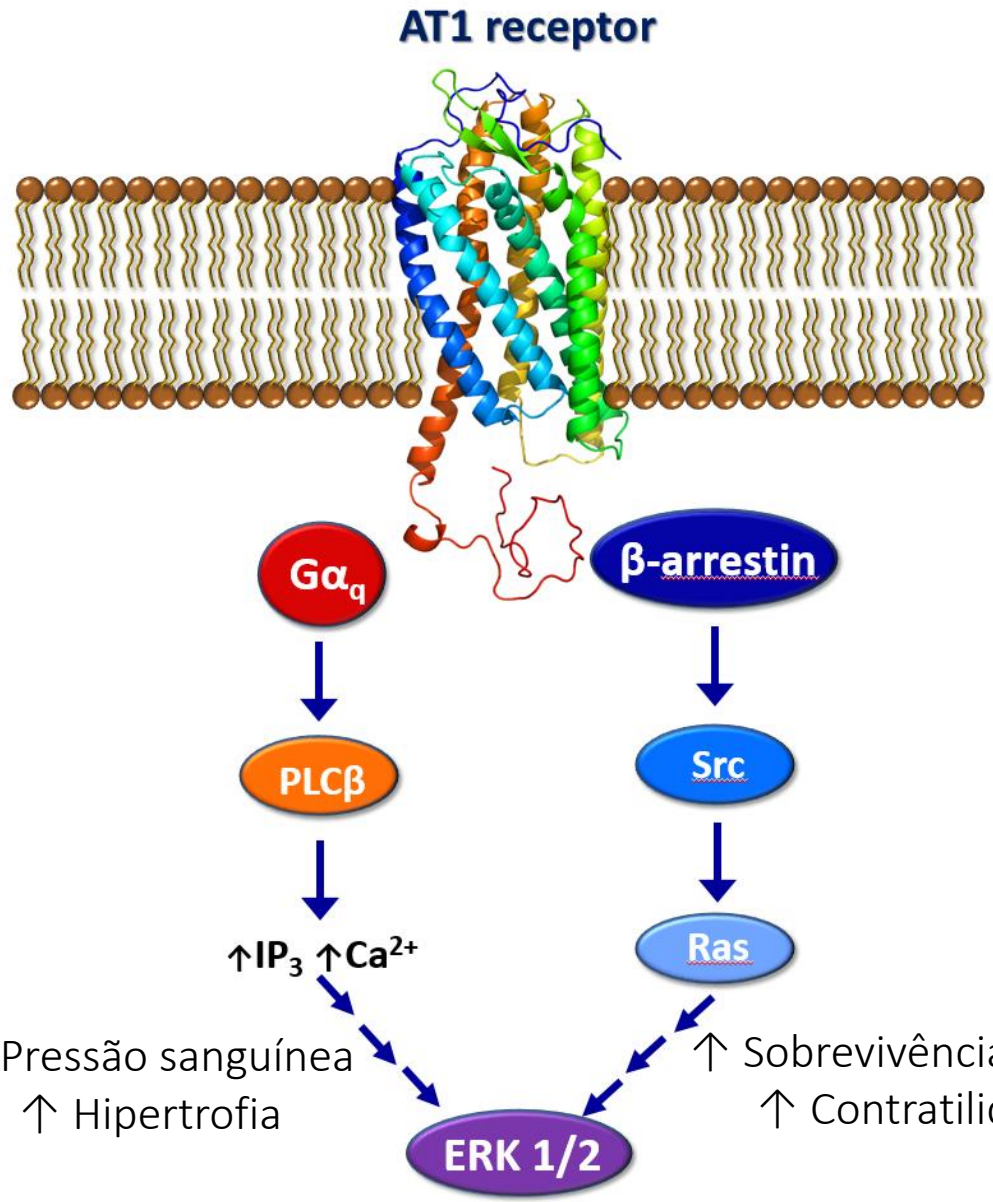
4°. Workshop de High Performance Computing – Convênio: USP – Rice University

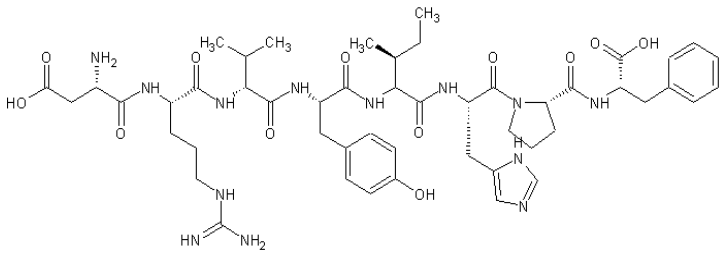
São Paulo, 17 de Outubro de 2016

Mestrando:
Silvestre Massimo Modestia

Orientadora:
Profa. Dra. Carlota de Oliveira Rangel-Yagui

Introdução

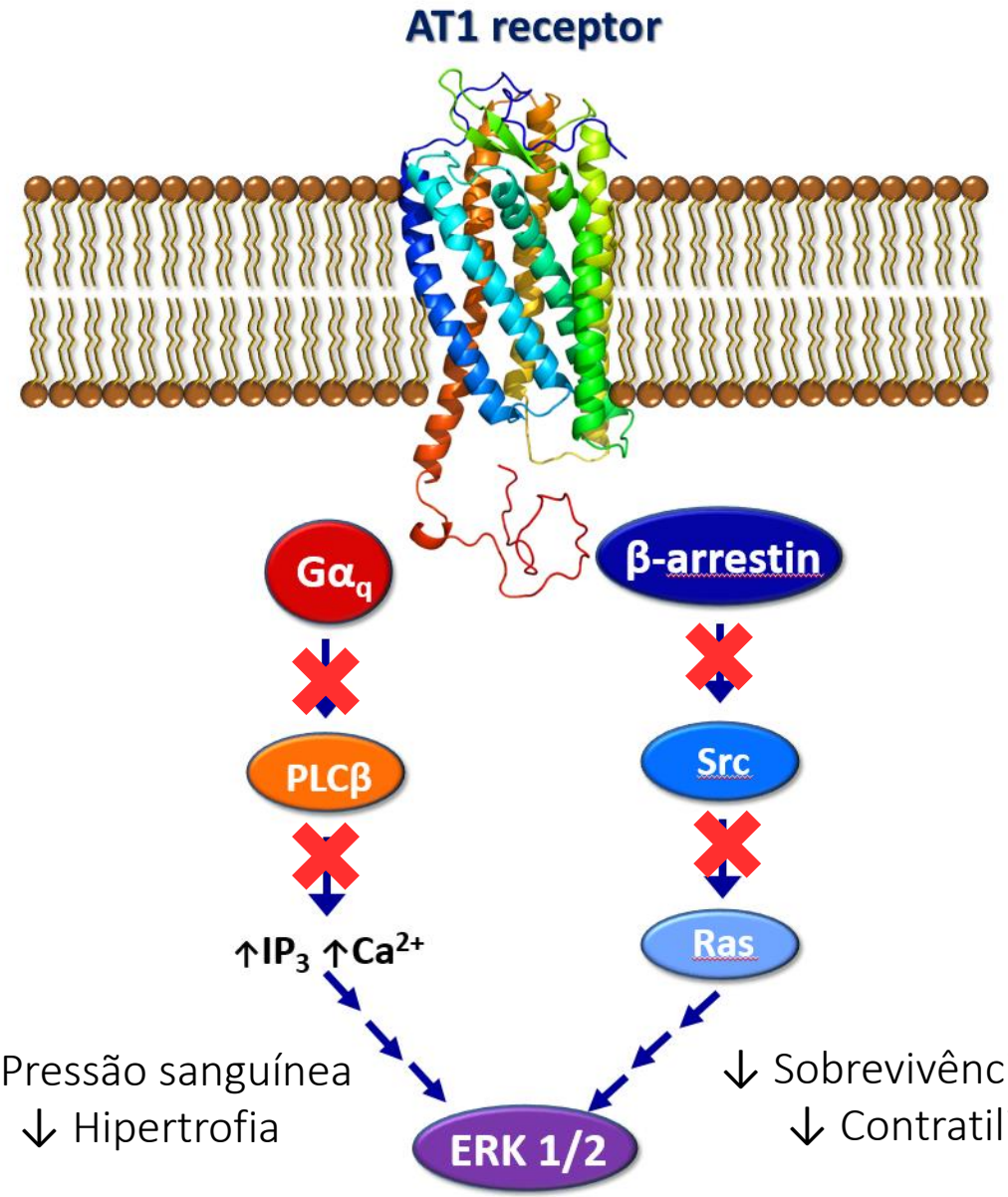


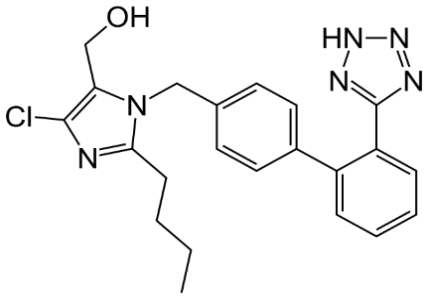


Agonista total (Angiotensina II)

Violin *et al.*, J Pharmacol Exp Ther, 2010

Introdução

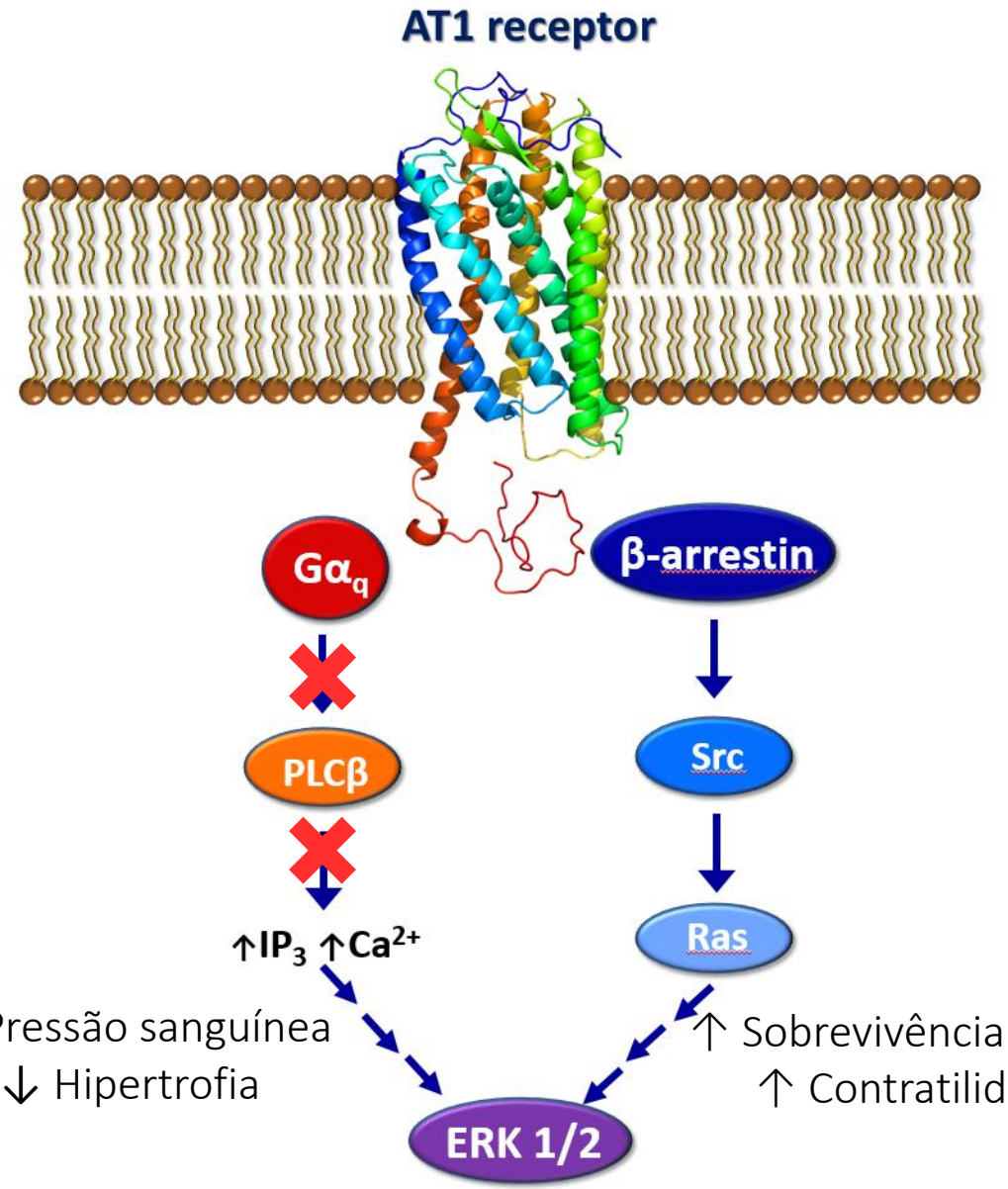


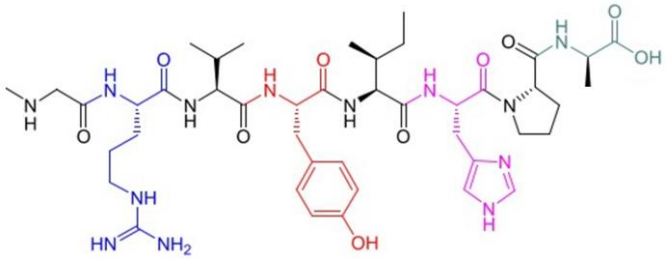


Antagonista (Losartana)

Violin *et al.*, J Pharmacol Exp Ther, 2010

Introdução





Agonista enviesado (TRV27)

Nova abordagem

Violin *et al.*, J Pharmacol Exp Ther, 2010

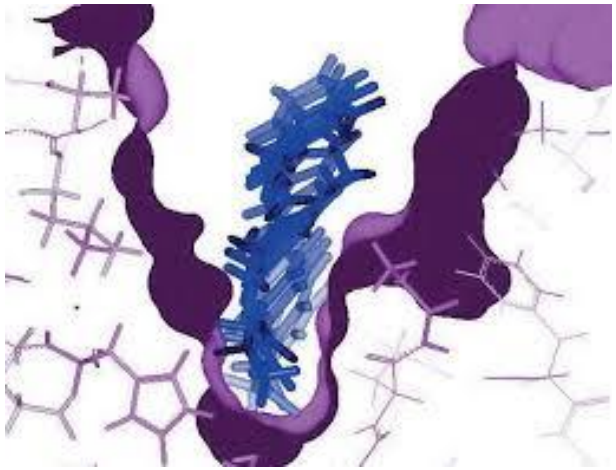
Introdução

Modelagem Molecular

Ancoramento Molecular (*docking*)

➢Predição da conformação de um ligante no sitio de um receptor.

- Método de amostragem.
- Predição de afinidade.

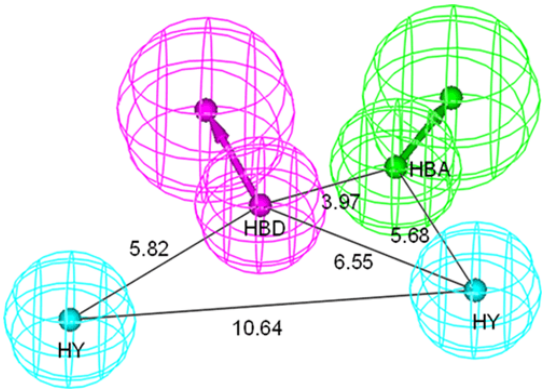


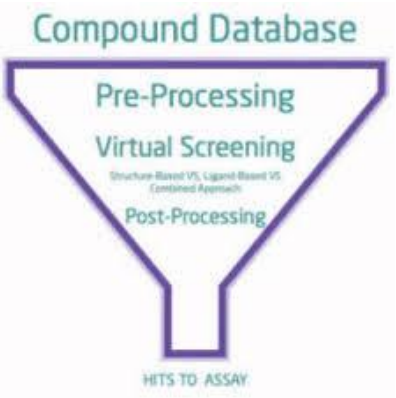
Dinâmica Molecular (DM)

➢**Campo de força:** Conjunto de parâmetros e funções usadas para descrever a energia potencial de um sistema.

$$E_{tot} = E_{str} + E_{bend} + E_{tors} + E_{vdW} + E_{elec} + \ldots$$

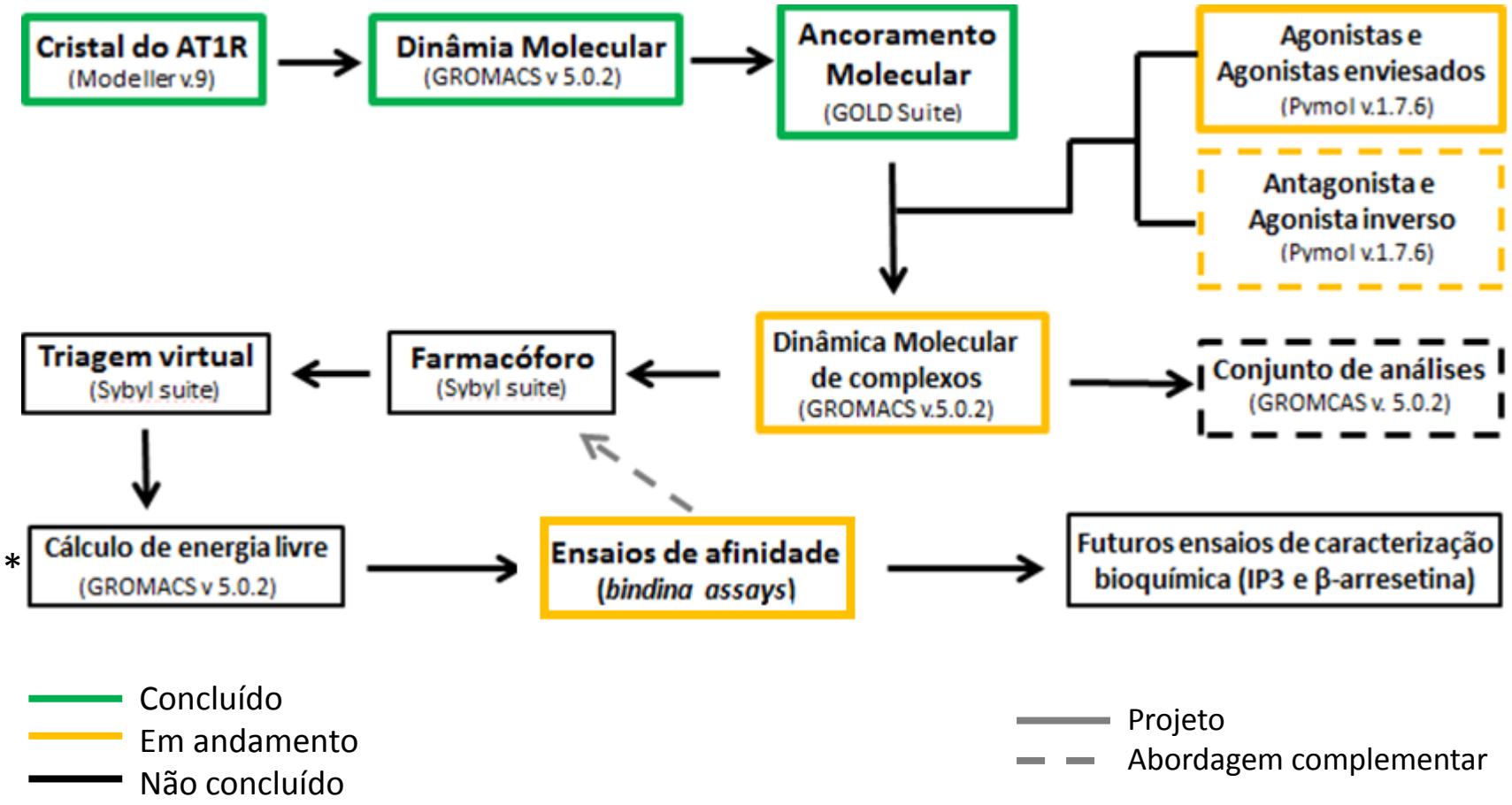
Farmacóforo e Triagem virtual





Objetivo

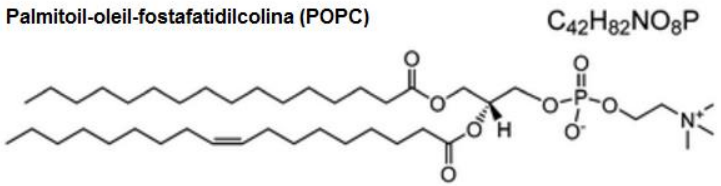
Planejamento de ligantes não peptídicos com atividade agonista enviesada para o receptor AT1.

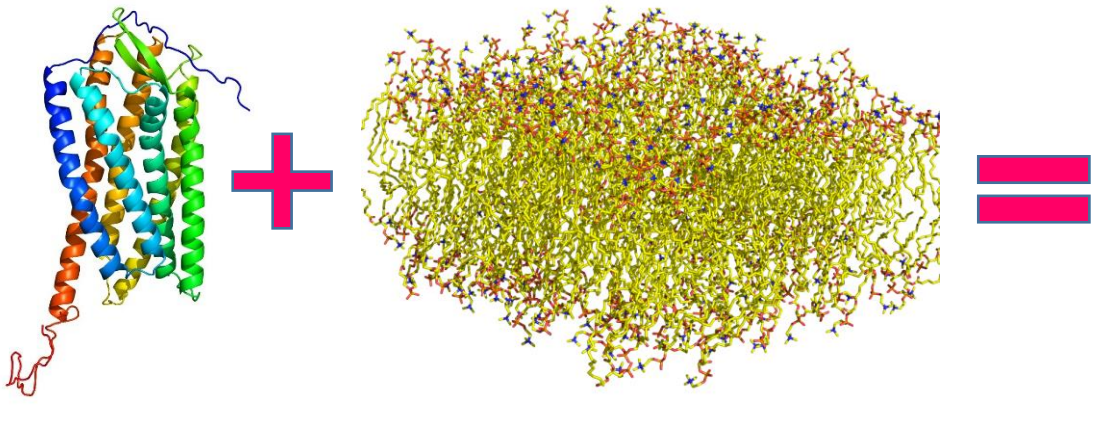


Metodologia

Dinâmica molecular (DM)

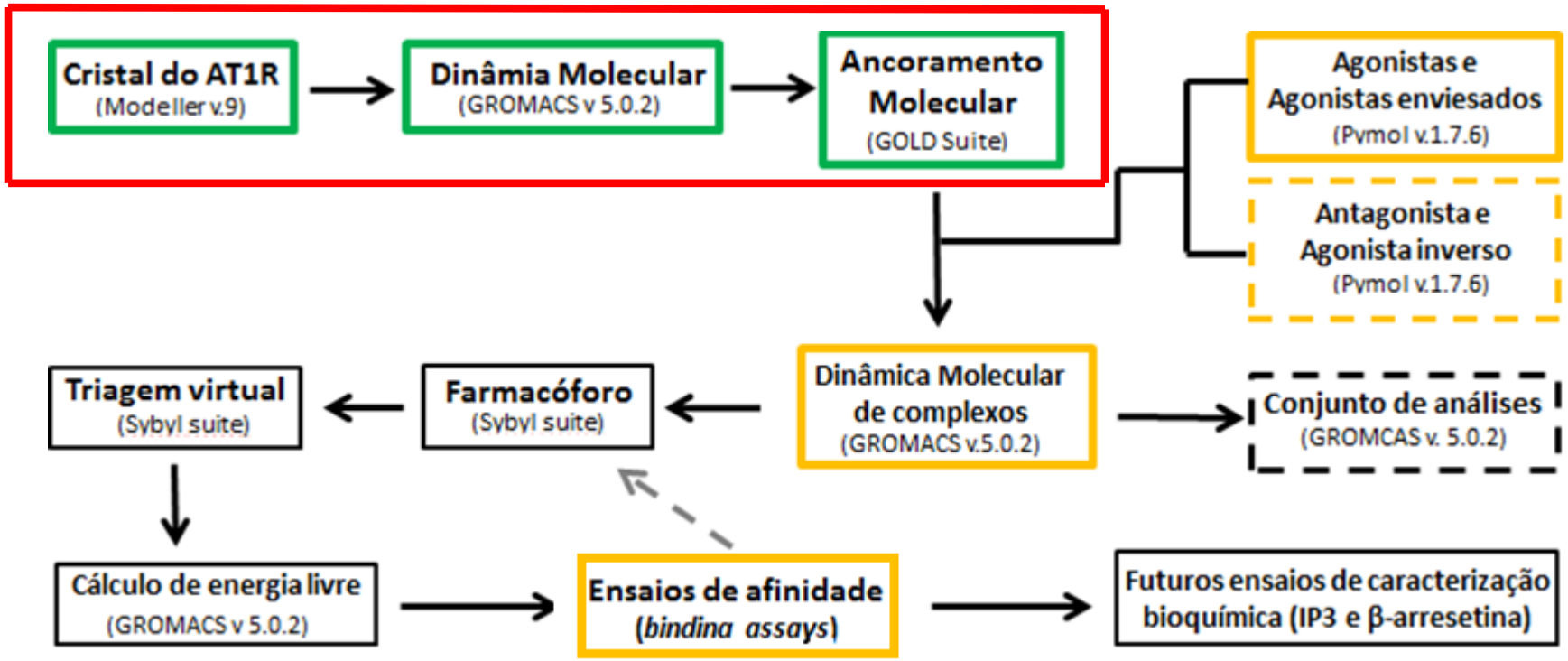
- GROMACS v. 5.0.5 (Abraham *et al.,* 2015).
- CHARMM36 (Best *et al.,* 2012).
- *High Performance Computing*, HPC-USP.
- Bicamada de POPC (Klauda *et al.,* 2010).
- InflateGRO (Kandt *et al.*, 2007).
- 10 simulação de 200 ns = 2 µs.



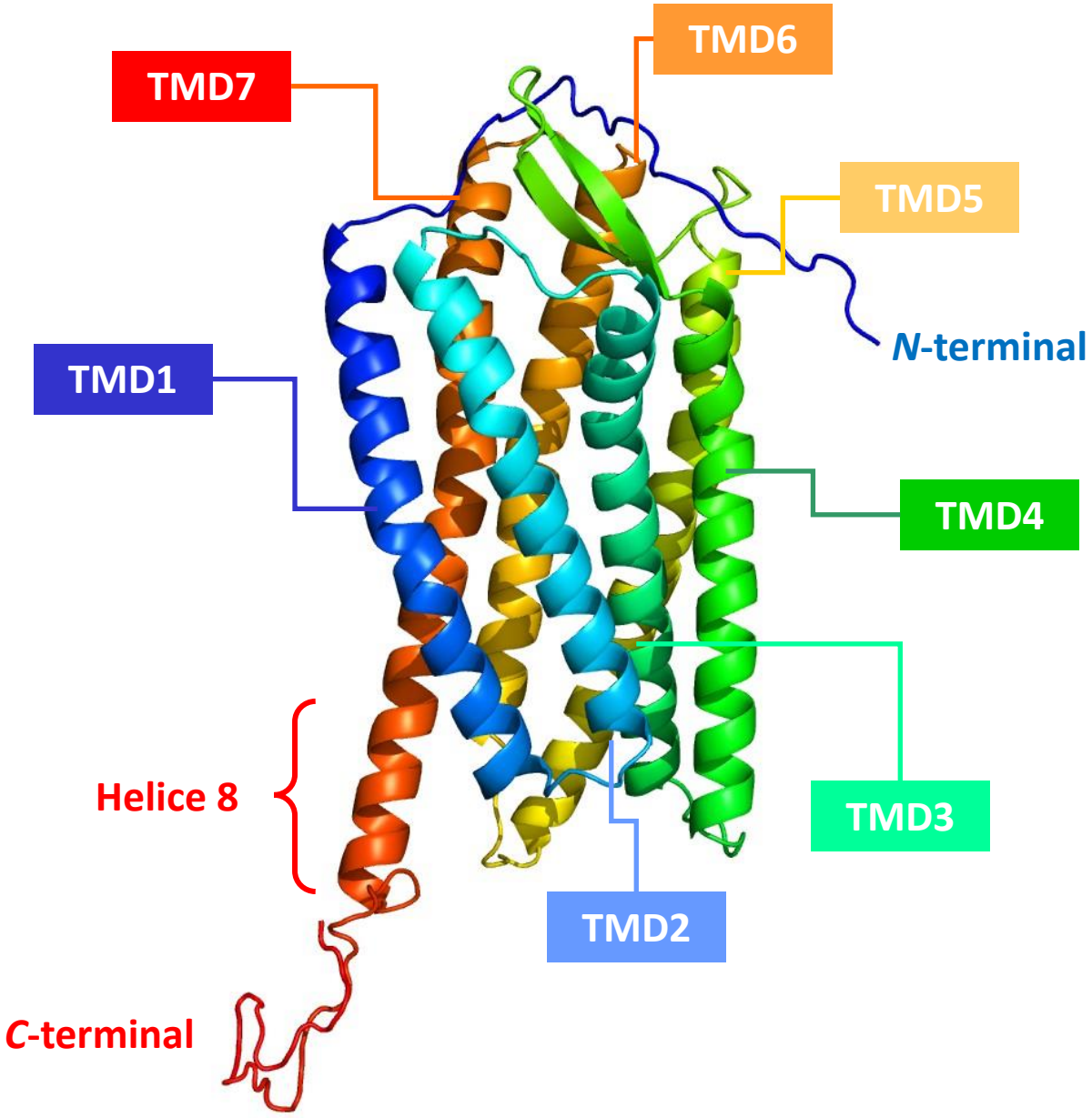


Resultados Parciais

Resultados Computacionais



Estrutura do receptor completo



Resultados Parciais

Dinâmica Molecular

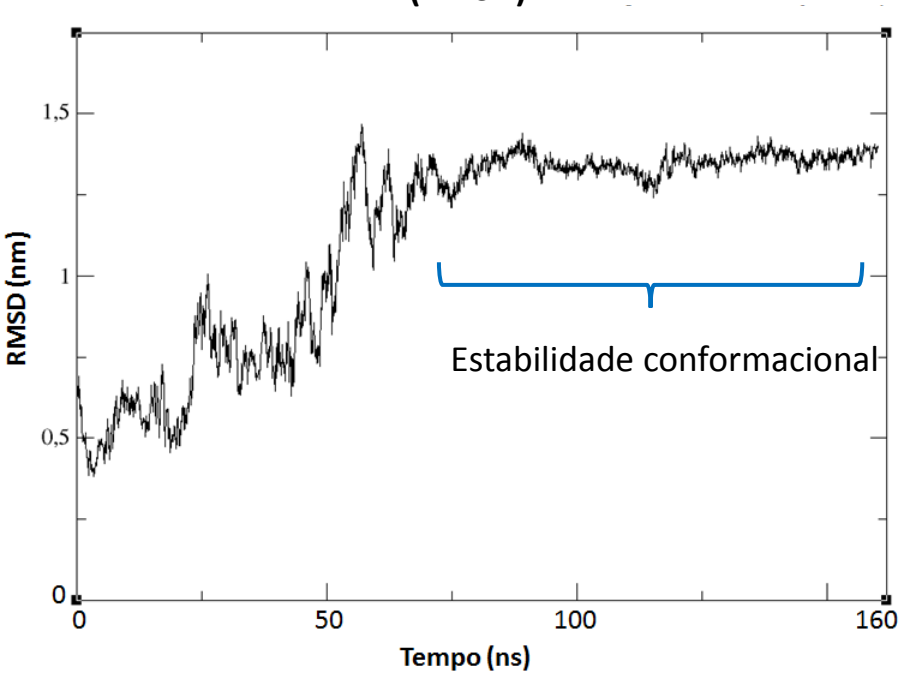
$$RMSD(t) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(x_i(t) - x_i(0)\right)^2}$$

N = Número de átomos i = posição atômica

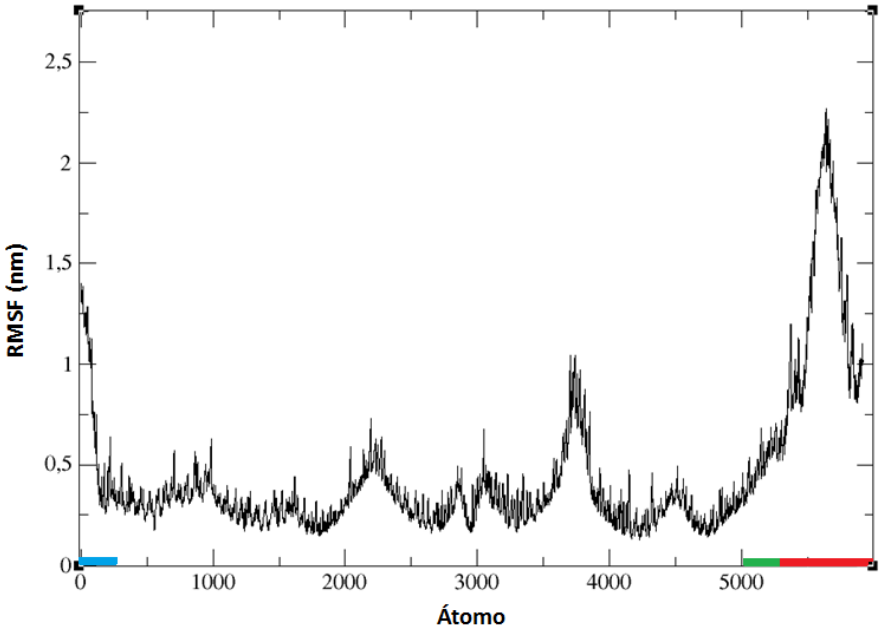
$$RMSF(i) = \sqrt{\frac{1}{T}\sum_{t=1}^{T}\left(x_i(t) - \bar{x}_i\right)^2}$$

T = Número de frames i = posição atômica

Gráfico de desvio quadrático médio das posições atômicas (RMSD)



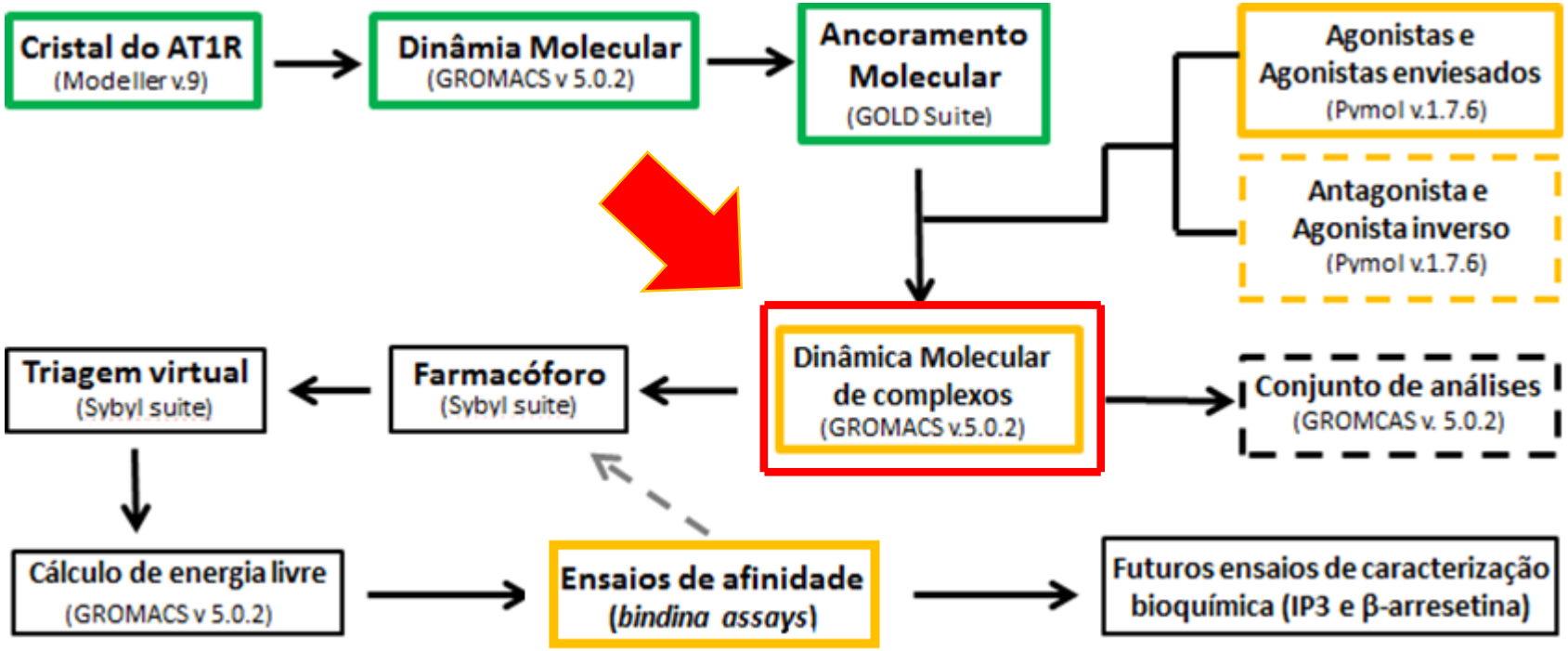
Flutuação do Desvio Quadrático Médio (RMSF)



N-terminal *C*-terminal

Resultados Parciais

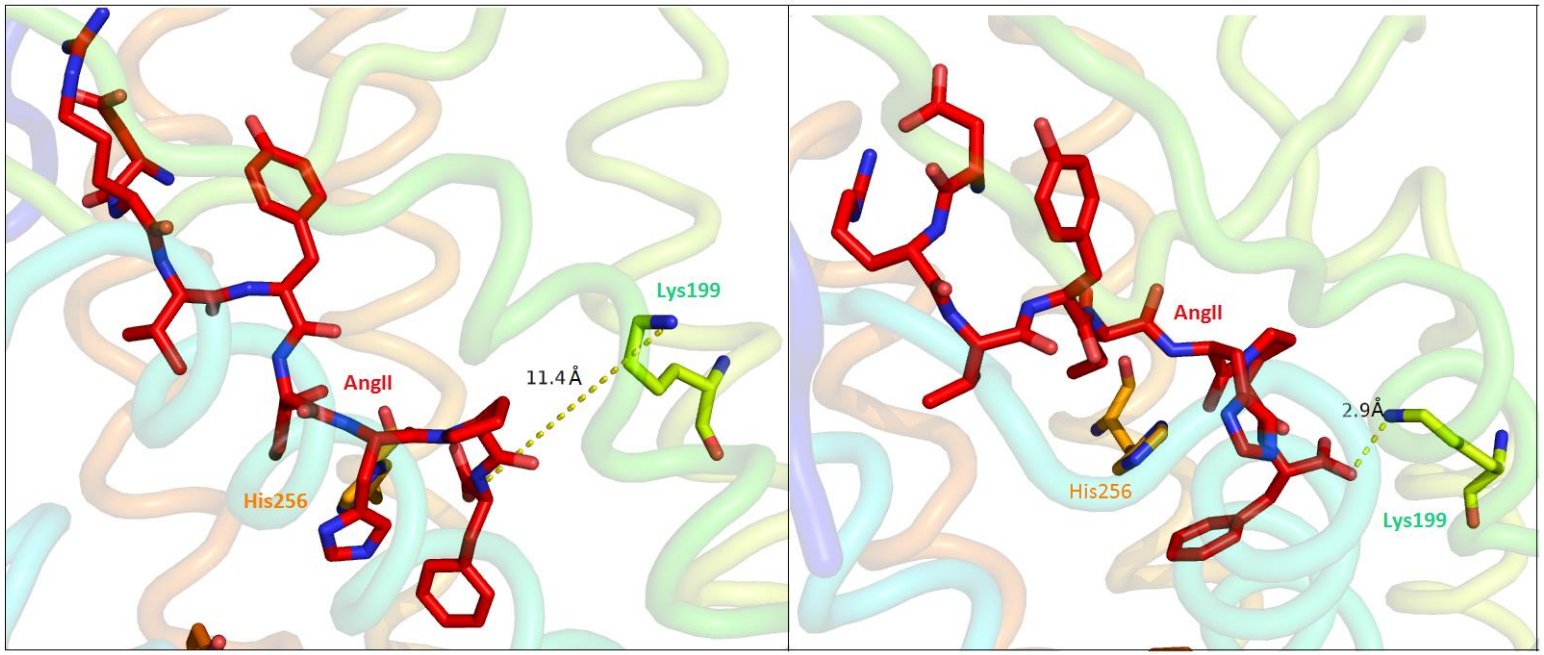
Resultados Computacionais



Resultados Parciais

Simulated Annealling

0 ns **3 ns**



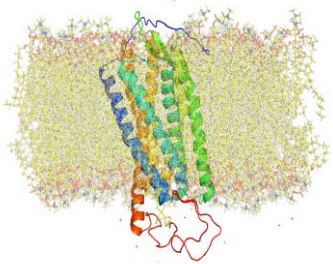
Tempo (ps)	0	200	400	500	600	700	800	900	1000	1200
Temperatura (K)	310	600	700	800	700	600	500	450	400	310

Kirkpatrich *et al.*, Science, 1983

Outros projetos

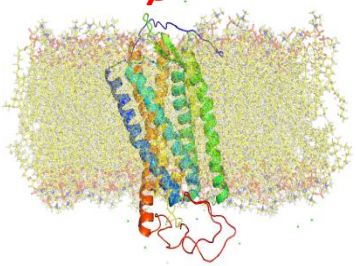
Força

Shear stress

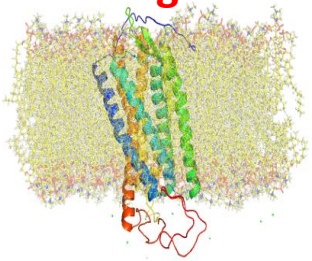


Ligantes

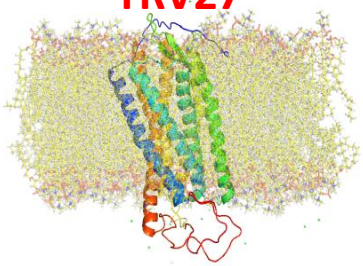
Ø



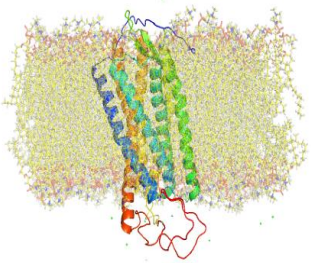
AngII



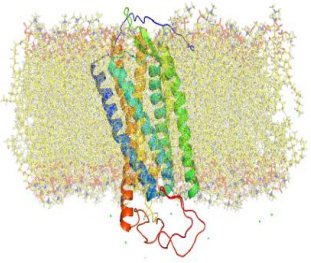
TRV27



Losartana

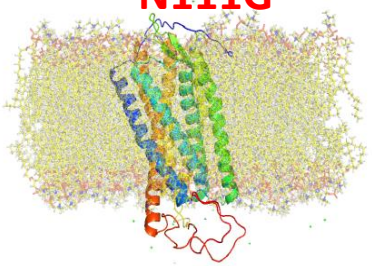


Olmesartana

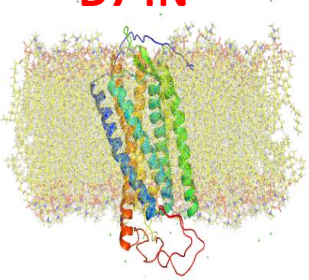


Mutantes

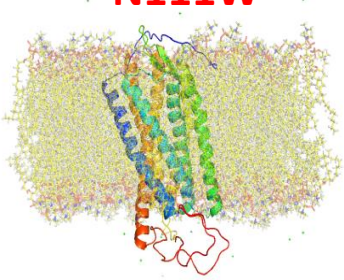
N111G



D74N



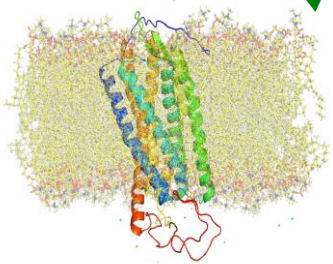
N111W



Outros projetos

?

Shear stress



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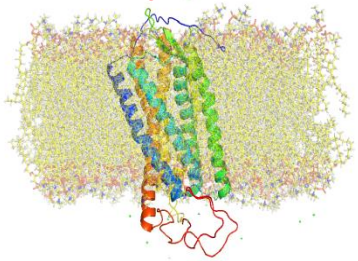
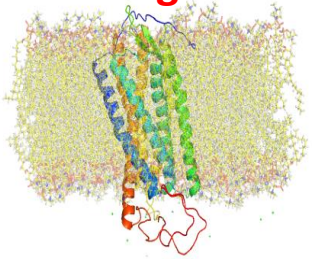
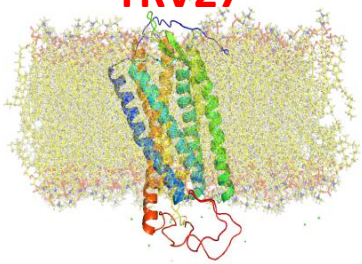


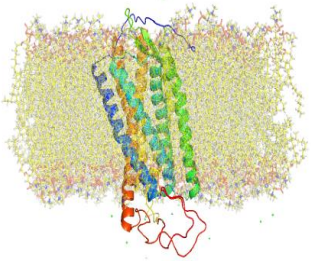
AngII



TRV27



Losartana



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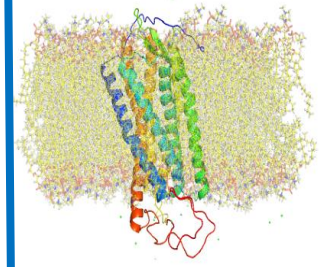
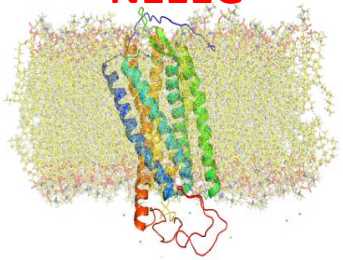
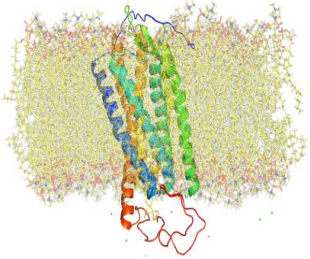


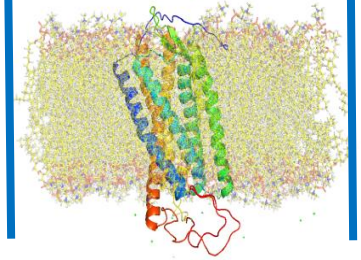
N111G



D74N

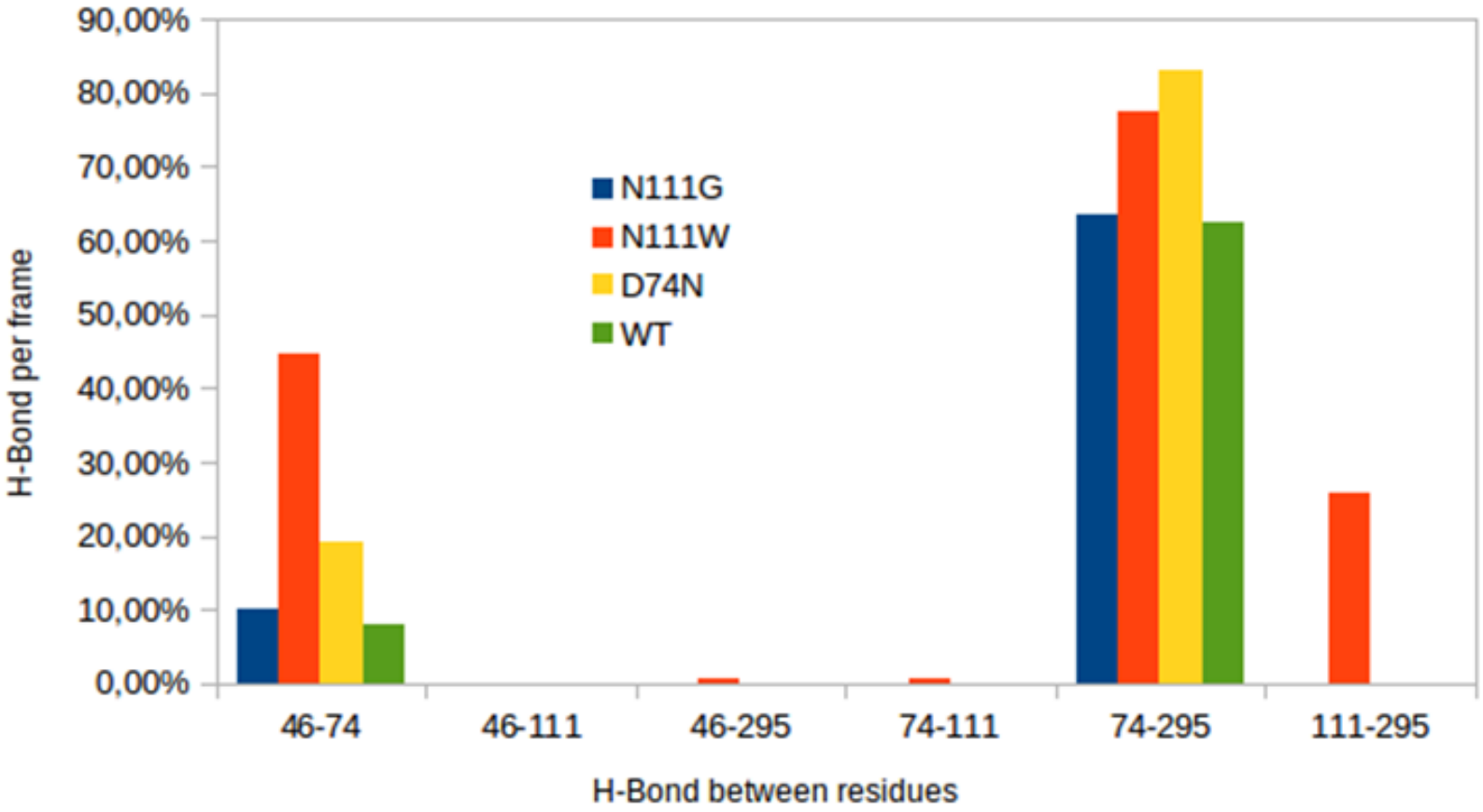


N111W



Resultados Parciais

N111G – Constitutivamente ativo
N111W – Inativo
D74N – Ativo para via da β-arrestina apenas
WT – *Wild type* (sem mutação)

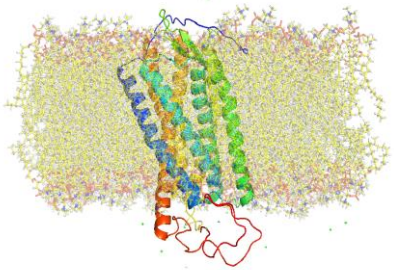


Uso e performance - Lince

Sistema completo – AT1R + Membrana + água e íons

```
               Core t (s)   Wall t (s)        (%)
       Time:  5192111.308   325972.223     1592.8
                         3d18h32:52
                 (ns/day)    (hour/ns)
Performance:       26.505        0.905
```

AT1R

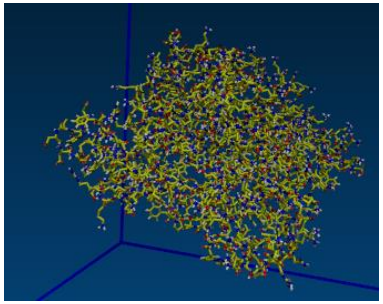


5 gb gerados para cada 100 ns simulados

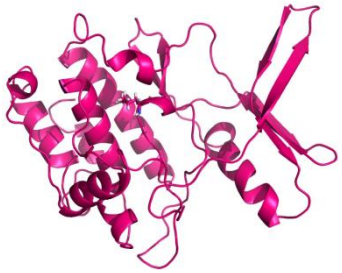
Projeto AT1R – 500 gb utilizados até agora (sem as análises)

Outros projetos

```
[smmodestia@lince:/scratch/smmodestia/Lince]$ du -h
588K    ./charmm36.ff
13G     ./2WID
330G    ./ASNase
66G     ./MYLK/P1588L
134G    ./MYLK
982G    .
```



2WID



MYLK

Em torno de 1 terabyte ocupado no momento!

Agradecimentos

HPC - High Performance Computing









HC FMUSP

InCor HC Zerbini Ciência e Humanismo

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico