Monte Carlo Simulation of Type IV Collagen Network Organization

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Introduction

- Type IV collagen (Figure 1) is found exclusively in basement membranes where it forms networks that provide much of the membrane's mechanical support.
- There are 2 different types of collagen IV networks: major and minor which have different properties (Table 1)

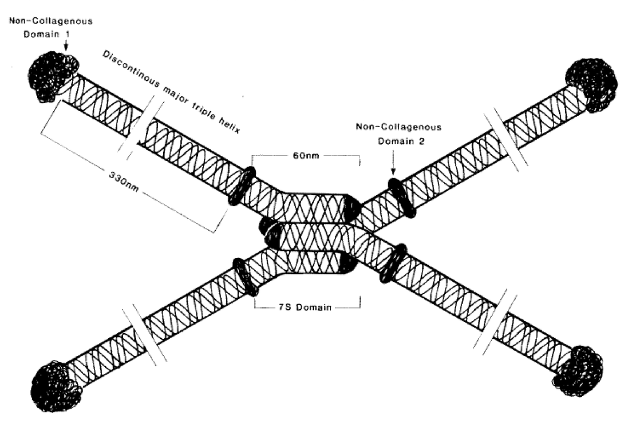

Fig1. Structure and function of collagen IV molecules. [1]

Property	Major network	Minor network
Location	All basement membranes	Select basement membranes
Intramolecular interactions	Less bonding	More bonding
Lateral interactions	Less cross-links	More cross-links
Relative concentration	Tissue-dependant	Tissue-dependant

- It is believed that the minor network is more stable and stiffer.
- An experimental analysis of the macroscopic changes occurring in collagen IV networks due to differences in molecular properties is very hard to perform.
- ***Objective: Use a Monte Carlo simulation to determine the influence of molecular differences on the collagen IV network properties***

Methods

- Collagen IV molecule modeled as a chain of springs placed on a 826x826 grid (Figure 2). Simulation space includes 1000 molecules that are randomly placed on the grid at the beginning.

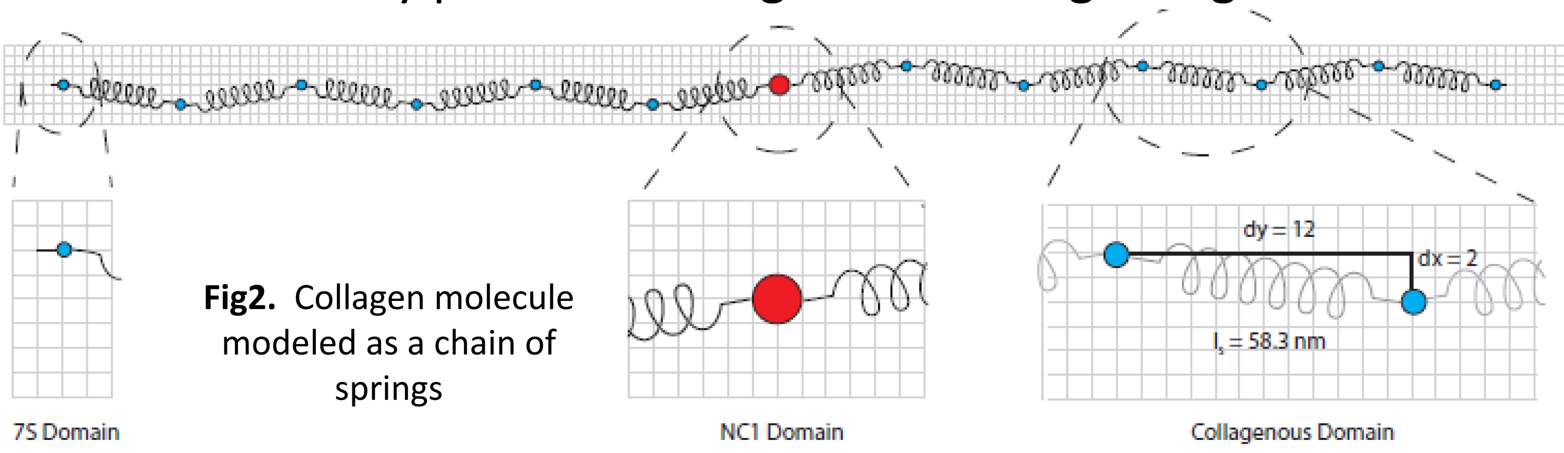

Fig2. Collagen molecule modeled as a chain of springs

- Three different simulation performed: Major-chain only, Homogeneous (no difference between networks), and Lateral (Minor network has a higher probability for lateral interactions). (Table 2)

Simulation	Interaction Energy (k_BT)			
	7S	Major: Major cross-link	Major:Minor cross-link	Minor:Minor cross-link
Major Networ	-5	-1	N/A	N/A
Homogeneous	-5	-1	-1	-1
Lateral	-5	-1	-1	-3

- Nodes are selected at random and an attempt is made to move to a neighboring position. Energy is calculated for the new and old position based on spring stretch (Equation 1)
- Moves are approved or rejected to minimize the energy of the system.

$$\frac{U_s}{k_B T} = \kappa_s (l - l_0)^2$$

- Eight simulations were completed for each network. Data is presented as average values ± SD of the network properties at equilibrium.

Results

- **Networks at equilibrium**

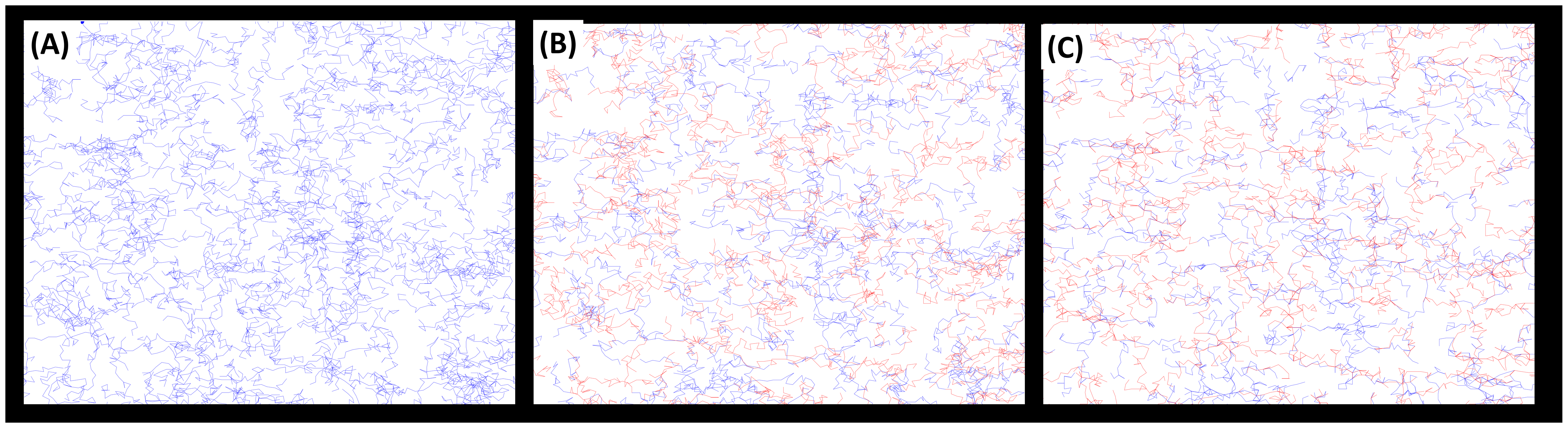

Fig3. Sample visual representation of the three different collagen IV networks at equilibrium. **(A)** Major-only network. **(B)** Homogeneous network. **(C)** Lateral network. Blue – Major network. Red – Minor network.

- **Network Properties**

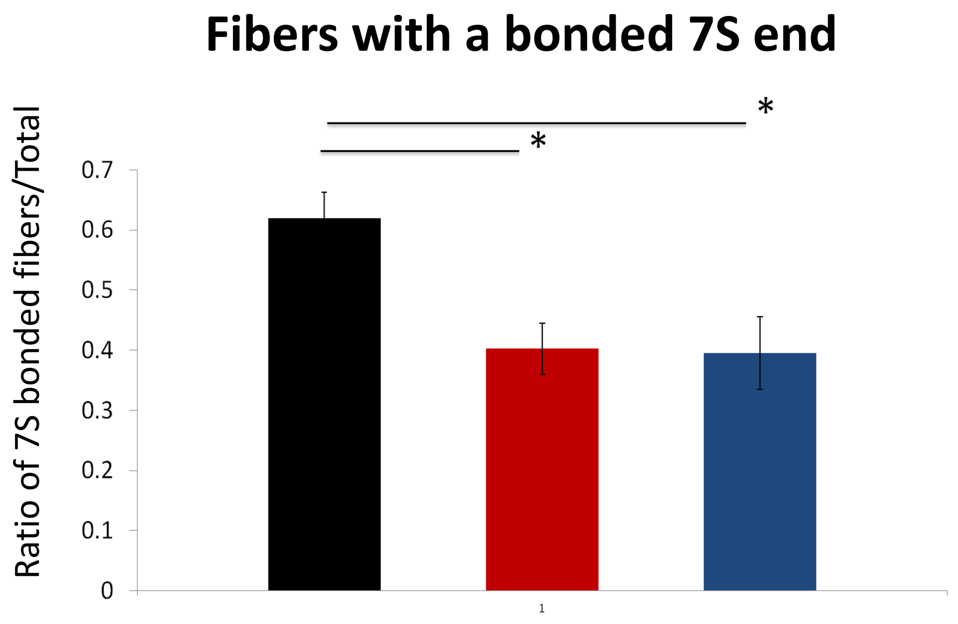

Fig4. 7S bonding ability of each network. Black – Major-only network. Red – Homogeneous network. Blue – Lateral network. There was a statistically significant difference between the Major-only network and the other 2 networks (p<<0.1).

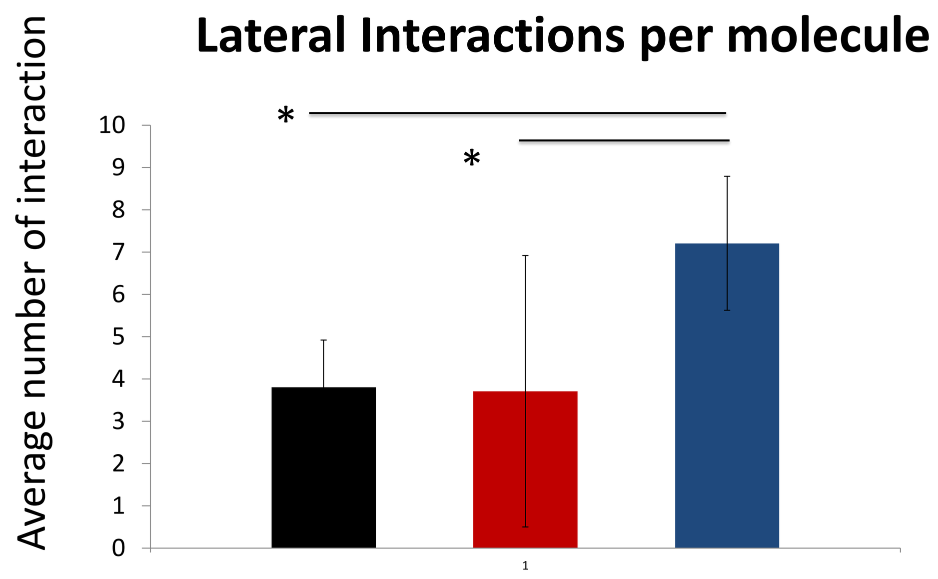

Fig5. Lateral bonding ability of each network Black – Major-only network. Red – Homogeneous network. Blue – Lateral network. There was a statistically significant difference between the Lateral network and the other 2 networks (p<0.1).

For N=8 simulations, the average ratio of bonded 7S ends and average number of Lateral interactions behaved as expected: number of bonded 7S ends was highest for the Major-only network and number of lateral interactions was highest for the Lateral network.

Conclusion

- The visual representation of the simulated collagen IV networks resemble the organization of an *in-vivo* collagen IV network (Figure 6)
- The molecular differences between the three networks resulted in significant macroscopic differences with mechanical implications:
  - The larger number of lateral interactions possibly stabilizes the Lateral network and makes it stiffer.
  - However, the increase in number of lateral interactions per fiber resulted in a decrease in molecules bonded at their 7S ends.
- It would be further interesting to test the differences in pore size for the three networks since filtration is an important function of basement membranes
- Extending the simulation to 3D space would allow to simulate mechanical stretch to better understand the changes in mechanics due to molecular differences.

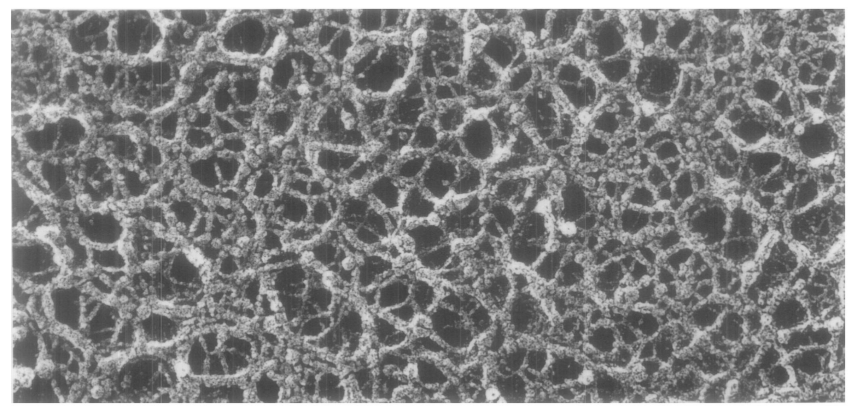

Fig6. An electron microscopy image of a collagen IV network. Source: Barnard K., et al., *1992*

Acknowledgements

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References

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