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Dear Dr. Rodley:

Well, you are certainly trying hard but you'll have to do a lot better before most people will believe it, if only because your structure is so ugly (though ingenious) and ours is so pretty! However you are quite right that while the base-pairing is well established and there's no doubt the chains run in opposite directions, the details of the structure are less well supported. For the reasons that Aaron Klug set out in his letter of 25 March to Richard Bates I don't think much of most of the general diffraction agruments that you are using. Nor am I impressed with a series of weak bits of evidence or plausibility arguments. What we need is a striking experiment that everybody will be able to recognize as correct. So far I have been only been able to think of two.

1) If your structure were really side-by-side, then a relaxed unnicked circular DNA should, on melting, come apart into two separate circles. This could easily be shown with present techniques using SV40, polyomer or better still, a deletion mutant with a smaller size. You should consult the two papers, by Depew and Wang, and by Pulleybank et al in PNAS (1975) 72, 4275----4284, and the other papers (for example, by Keller) quoted there. They show the Gaussian distribution of L (see my PNAS (1976) 73, 2639) produced by temperature. For a true SBS structure one of those relaxed, or nearly relaxed bands, would, on denaturing give two separate chains, as is indeed found for a circular DNA with one nick in it but is not found if both chains are intact. (The sedimentation co-efficients are very different -- consult the literature.) This would be a completely convincing demonstration of the general truth of your idea and a disproval of our structure.

Unfortunately your structure, as described, is not exactly SBS but has a slow twist in it. To prove this idea (which, incidentially, is surely less "appealing" than a true SBS) you have to use ethidium bromide plus the nicking-closing enzyme, etc., to produce a "supercoiled" molecule for which L has been reduced from the small value you predict to zero. This is possible but rather harder work.

I must stress, however, that without this evidence no hard-headed molecular biologist is likely to believe your idea so I suggest you promote this type of experiment instead of trying to prove your structure with a lot of rough model building and rather doubtful mathematics.

2) The only other way I can see that would carry conviction would be to obtain (largish) quantities of a short (10 to 15 bp) stretch of DNA with a defined sequence -- preferably with a couple of G-C pairs at each end, crystallize it and solve the structure by isomorphous replacement to a highish resolution -- in effect what was done for tRNA (which, please note, in spite of your remarks about irregular backbone arrangement, etc., has no trace of your structure and plenty of the double helix predicted by the fibre x-ray work. But one must concede this is RNA, not DNA). The best way would be for someone to synthesize such a DNA (as Khorana does) for then an unusual base or two could be included to which a heavy atom could conveniently be attached. The main points are that the structure should be solved, by isomorphous replacements, without any assumptions about helices or SBS and that the resolution should be adequate. (Both conditions were fulfilled for the tRNA crystals.) I realize that this is not easy but without such data who will believe your detailed model, even if the first experiment were to work.

I should stress that we are concerned with the (approximate) configuration of "normal" DNA in solution. As I explained previously, if the double helix is correct in solution then your model cannot be correct for most of the DNA on the nucleosome, because the $|\Delta L|$ between the two is too small. Whether your model ever occurs in special circumstances is another matter which we can, I feel, usefully postpone for the moment.

Finally I should add that John Cairns has written to me that Wally Gilbert claims that your model has already been disproved because "D-loops remove exactly the right number of supercoils for the classical B form model". I know what a D-loop is -- it occurs in the replication of mitochondrial DNA and possibly elsewhere -- but at this moment I cannot put my hand on the evidence Gilbert quotes. However I hope to track it down, possibly when I am at Cold Spring Harbor in early June, and if I do I will let you know.

Forgive me for being so discouraging. I will be most surprised if your model turns out to be correct but you have done a useful job (more useful than Donohue did) in pointing out the rather fragile nature of some of the x-ray evidence.

Yours sincerely,

F. H. C. Crick
Ferkauf Foundation Visiting Professor

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